STUDY TO ASSESS THE REQUIREMENT OF A ROUTINE UPPER GI CONTRAST STUDY POST-OPERATIVELY IN PATIENTS UNDERGOING AN OESOPHAGEAL ANASTOMOSIS – A RANDOMIZED CONTROL TRIAL

A dissertation submitted to the M.G.R. Medical University, Tamil Nadu – in partial fulfillment of the requirements for the M.S. Branch I (General Surgery) examination held in April 2016.

CERTIFICATE

This is to certify that this dissertation entitled "**STUDY TO ASSESS THE REQUIREMENT OF A ROUTINE UPPER GI CONTRAST STUDY POST-OPERATIVELY IN PATIENTS UNDERGOING AN OESOPHAGEAL ANASTOMOSIS – A RANDOMIZED CONTROL TRIAL**" is a bonafide work done by Dr. Niveditha Shama Viswanathan under our guidance and supervision in the Department of Surgery, Christian Medical College, Vellore, submitted for the M.S., (General surgery) branch 1 examination to be held in April 2016, by the Tamil Nadu Dr. M. G. R. Medical University, Chennai.

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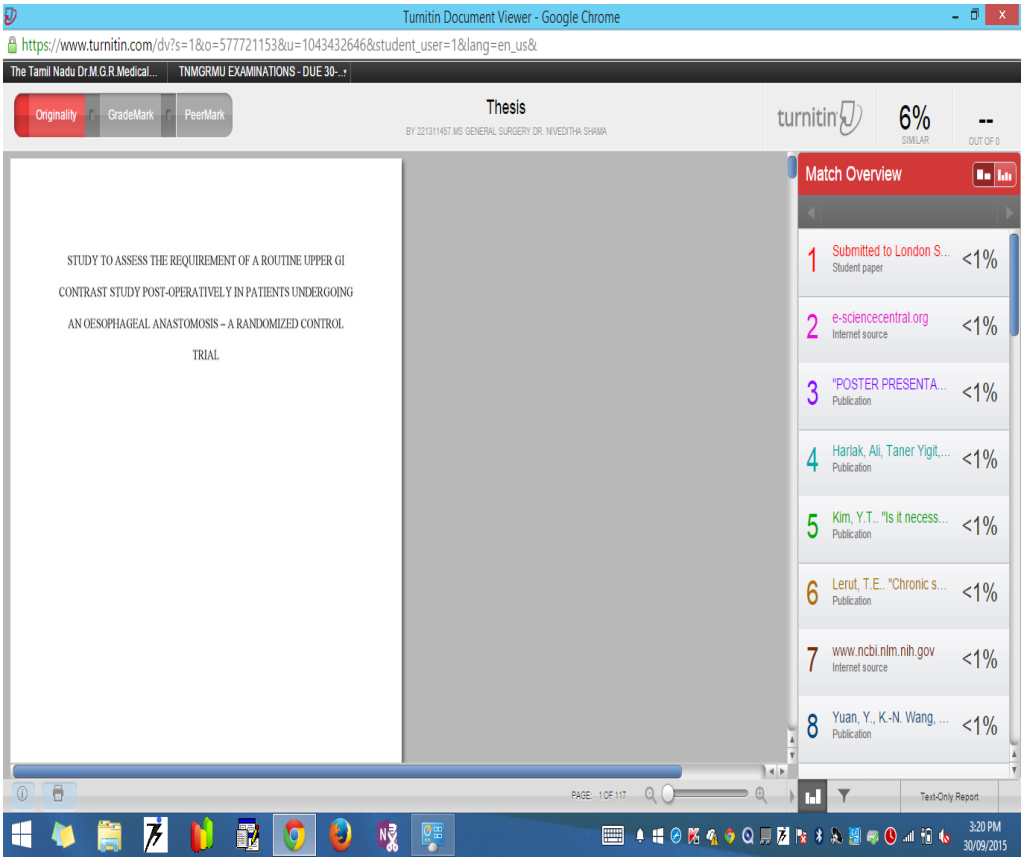

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CONTENTS

1. ABSTRACT

TITLE OF THE ABSTRACT: Study to assess the requirement of a routine upper GI contrast study post-operatively in patients undergoing an oesophageal anastomosis – a randomized control trial.

DEPARTMENT **:** General Surgery, Unit III, CMC, Vellore

NAME OF THE CANDIDATE : Dr. Niveditha Shama Viswanathan

DEGREE AND SUBJECT : M.S. General Surgery

NAME OF THE GUIDE : Dr. Inian Samarasam

OBJECTIVES:

1. To compare the delay in starting oral feeds, liquids and solids, duration of post-operative hospital stay and to compare readmission and re-surgery rates.
2. To evaluate the overall morbidity and 30 day mortality in the two groups.

METHODS:

A prospective randomized control study was carried out to assess the need of a routine upper GI contrast study after an oesophageal anastomosis. All patients undergoing an oesophageal anastomosis were randomized into 2 groups.

The patients from Group A underwent a routine upper GI contrast study between post-operative day 5 to day 7. None of the patients from Group B underwent a routine upper GI contrast study. However, they underwent an appropriate radiological assessment post operatively, if a leak was suspected. The outcomes were assessed as per objectives.

RESULTS:

Among the 40 patients recruited, it was found that there were no significant differences in length of hospital stay and the time to starting liquid feeds orally between the 2 groups. However, there is a probable statistically significant delay of 1 day in starting solid feeds. There was no added morbidity in the non-contrast study group. Thus, it can be concluded that the practice of doing a routine upper GI contrast study after an oesophageal anastomosis may not be necessary unless there are strong indicators to perform it. Instead, monitoring the patient's clinical parameters to look out for clinical evidence of a leak, followed by performance of an appropriate investigation to confirm or rule out a leak may be a more appropriate practice.

2. INTRODUCTION:

2.0 INTRODUCTION:

In patients undergoing an oesophageal anastomosis, post-operatively**,** a routine upper GI fluoroscopic imaging with thin Barium Sulfate/ Gastrografin has been employed to assess the integrity of the anastomosis, prior to initiation of feeding orally. However, this modality is plagued by a low sensitivity, and its routine use has been questioned in the last decade. The aim of this study was to assess outcomes between a group who had the routine upper GI contrast study and a group where a routine contrast was not performed. .

2.1 BACKGROUND DATA:

A number of retrospective studies have been carried out to assess the need of doing a routine upper GI contrast study on the 7^{th} postoperative day following an oesophageal anastomosis. In most of the studies published, only 70% of anastomotic leaks were detected within the first five days.(1) Moreover, even if the upper GI contrast study done on day 7 was normal, this did not preclude a delayed leak occurring as late as one month after surgery (maximum period). This resulted in delayed leaks being missed out and a consequent delay in intervention.

2.2 CURRENT LITERATURE:

Anastomosis of the oesophagus to the stomach or jejunum or colon is done widely in many surgical conditions like oesophageal cancer, gastric cancer, after resection of oesophageal or gastric strictures (due to corrosives) etc. Prior to starting oral feeds, post operatively, the routine practice has been to carry out an upper GI contrast study

as a screening procedure for anastomotic leaks. This practice is still followed by many centers, including ours. However, studies have suggested a poor sensitivity and high false negative error rate of this test. In a series with clinical anastomotic leak rate of 9%, it was found that the test was insufficient to be worthwhile as a screening procedure(2)(3).

A study series further went on to show that 56.3% of anastomotic leaks were diagnosed without contrast studies. Contrast studies changed clinical management correctly in only 2 of 132 patients, while failing to diagnose 4 of 7 possible leaks. Hence the indication for a routine upper GI contrast study was questioned.(4)

Further studies have proven that, post operatively upper GI contrast studies can be selectively done in patients with clinical suspicion and clinical signs of anastomotic leakage including sepsis, fever > or = 39.0 degrees C and leukocytosis > or = 20 x 10^9/ml. (5)(6) Currently, there is proof to suggest that a routine upper GI contrast study has minimal impact in the postoperative management of patients undergoing oesophageal anastomosis.(7)

2.3 INDICATIONS FOR OESOPHAGEAL RESECTION AND ANASTOMOSIS:

Oesophageal surgery has evolved a long way since the early 1800s. The most common indications of oesophageal resection can be divided into benign and malignant causes. The common benign tumors are GISTs, leiomyomas, lipomas etc. The malignancies include adenocarcinomas, squamous cell carcinomas, etc. Other indications include benign strictures secondary to corrosive ingestion or certain drugs. In malignancies of

the oesophagus, surgery still remains the treatment of choice, backed by neo-adjuvant and adjuvant therapies.

2.4 OESOPHAGEAL RESECTION TECHNIQUES:

The oesophageal resections are performed in differing approaches and techniques depending on the type and the location of tumors. They include:

1. Two phase Ivor Lewis' Operation: Here the abdominal and thoracic cavities are opened together to excise the tumor and create a gastric tube to bridge the defect. This places the anastomosis in the thoracic cavity, thereby conferring an added risk of fatal mediastinitis in case of an anastomotic leak. This is preferred in middle and distal tumors or strictures.
2. Three phase McKeown's Operation: The third incision, apart from the thoracotomy and laparotomy, is placed in the neck to achieve a cervical anastomosis. This technique is preferred for proximal tumors.
3. Trans-hiatal Orringer's Operation: Here 2 incisions are made, a laparotomy and a cervical incision. This is usually adopted in lower oesophageal lesions. The lower portion of the oesophagus is mobilized via the laparotomy under direct vision through the diaphragmatic hiatus. The upper part of the oesophagus is mobilized through the cervical incision by blunt dissection. This technique obviated the need for a thoracotomy and the accompanying morbidity.

In strictures of the oesophagus secondary to corrosives or other etiologies, a bypass conduit is created using the stomach, colon or jejunum. This may be combined with an oesophagectomy. Proponents of oesophagectomy cite risk of malignancy, mucocele

formation and GERD as the reasons for resection. The counter argument to it is the possibility of dense peri-oesophageal adhesions resulting in tracheal injury, nerve injury, chyle leak etc. while attempting a resection.

Out of the three possible conduits colon, stomach and jejunum are favored in that order. The jejunum is least preferred due to short length and precarious vascularity. In many cases, concurrent gastric injury may occur following caustic ingestion, thereby making it unsuitable for use as a conduit. The colon is generally preferred as it has shown good results in terms of definite vascularity and luminal size match.

2.5 COMPLICATIONS FOLLOWING AN OESOPHAGECTOMY:

NON ANASTOMOTIC COMPLICATIONS:	ANASTOMOTIC COMPLICATIONS:
Pneumonia Arrhythmia Wound infection Empyema/effusion Reintubation Ventilator dependence Urinary tract infection Deep venous thrombosis/pulmonary embolus Wound dehiscence Recurrent laryngeal nerve injury Myocardial infarction Stroke Chylothorax Pancreatitis Pericardial effusion	Anastomotic leaks Anastomotic strictures Tracheo-oesophageal fistula secondary to leaks

2.6 DRAWBACKS OF CONTRAST STUDIES:

Upper GI contrast studies were practiced routinely after an oesophageal anastomosis to assess occult leaks. However, this practice has been falling out of rote gradually, due to the low sensitivity and high false negative rates which fail to predict late leaks. Apart from this, the 2 contrast materials used – Barium sulfate and Gastrografin – are accompanied by their own adverse reactions.

Barium, when aspirated into the airway tract remains there indefinitely and can predispose to granulomatous inflammation. Extravasation of barium into the peritoneal cavity can induce peritoneal reaction, associated with formation of granulomas and adhesions. Hence, Gastrografin is preferred to detect peritoneal leaks. However, aspiration of Gastrografin into the airway can cause pulmonary edema due to the hypertonicity.

Bearing in mind the low pick up rates of these contrast studies, it is questionable as to whether the routine use of these studies is warranted. This trial was carried out to assess the same.

3. AIMS AND OBJECTIVES

3.0 AIM:

To assess the requirement of a routine upper GI contrast study post-operatively in patients undergoing an oesophageal anastomosis.

3.1 PRIMARY OBJECTIVES:

1. To assess the delay in starting oral feeds, liquids and solids between the two groups.
2. To compare duration of post-operative hospital stay between the two groups.
3. To compare the re admission rates or re-surgery rates between the two groups.

3.2 SECONDARY OBJECTIVES:

1. To evaluate the overall morbidity and 30 day mortality in the two groups.

4. LITERATURE REVIEW

4.0 LITERATURE REVIEW:

Oesophageal and gastric cancers rank among one of the most common malignancies in India. In Asia, gastric cancer is the second-most common malignancy among men the third most common malignancy among females.(8) Oesophageal cancer is the eighth most common malignancy worldwide. (9)

On assessing trends of oesophageal and gastric cancers in India, there is a rising incidence of oesophageal malignancies and a relative, gradual decline in the incidence of gastric cancers.(10) Since this study included patients who had sustained upper GI injuries secondary to corrosive ingestion, incidence of the same was also assessed. India has a higher incidence of acid ingestion than alkali.(11)

4.1 RISK FACTORS FOR OESOPHAGEAL AND GASTRIC CANCERS:

Oesophageal and gastric cancers have a time tested and scientifically proven association with tobacco usage in various forms. In India, the different forms of tobacco usage include smoking cigarettes and bidis as well as chewing it as quid.(12) The incidence of oesophageal cancer was higher than oral cancer in tobacco chewers which was attributed to the practice of swallowing the liquid extract.(12) It was also detected that betel nut chewing without tobacco conferred an independent risk of developing malignancies of the aero-digestive tract including the oesophagus.(12) Another risk factor associated with upper gastrointestinal malignancies was alcohol consumption, with arrack consumption conferring the highest risk. (12) Acetaldehyde,

a byproduct of alcohol acts as a carcinogen and the synergistic activity of tobacco and alcohol consumption had a higher risk of developing cancer.(13) Other aetiological associations of gastric cancer include Helicobacter pylori infection, dietary and lifestyle associated factors like consuming salted tea, pickled food, rice intake, spicy food, soda additives in diet etc.(8)

The two most common malignancies encountered in the oesophagus are squamous cell carcinoma and adenocarcinoma. The incidence of squamous cell carcinoma is higher than that of adenocarcinoma and adenocarcinomas are more common in the lower one-third of the oesophagus in a setting of Barrett's oesophagus. Gastric malignancies are most commonly adenocarcinomas.(14) Gastro-oesophageal junction tumors are a special subset with unique properties and are mostly adenocarcinomas.

4.2 NATURAL HISTORY OF OESOPHAGEAL CANCER:

At presentation, many patients have locally or regionally advanced disease because of the lack of a serosal layer. One other reason is the rich submucosal lymphatic network, which results in local infiltration and rapid spread to loco-regional lymph nodes. The most common sites of distant disease are the lungs, liver and bones. The predictive factors for tumor dissemination include depth of tumor invasion and lymph node involvement.(14)

The median survival after an oesophagectomy for localized disease is 15 – 18 months. The overall 5 year survival rate after operation is 20– 25%. The patterns of failure depend on the location of the tumor as well as the histopathology. Tumors located in the upper two-thirds, which are predominantly squamous cell carcinomas, recur as

loco regional recurrences. Tumors located in the lower one-third, which are predominantly adenocarcinomas, recur with distant metastasis. Neo-adjuvant therapy in oesophageal cancers is shown to alter the patterns of failure as opposed to upfront surgery alone. (14)

4.3 CLINICAL PRESENTATION AND PREOPERATIVE EVALUATION OF OESOPHAGEAL CANCER:

The most common presentations of oesophageal cancer are dysphagia, which may signify locally advanced disease and weight loss. The dysphagia is usually progressive, with initial difficulty in swallowing solids followed by liquids. There may be past history of tobacco or alcohol abuse. Weight loss occurs in 90% patients and is associated with the dysphagia. Odynophagia, dull retrosternal pain, bone pains, cough etc. may signify metastatic disease.(15)

Preoperative evaluation includes an upper GI endoscopy and biopsy as a means of establishing diagnosis. Chest radiography and a contrast enhanced computed tomogram are also performed to delineate the site of disease, extent of disease and to stage it. FDG-PET (Fluorodeoxyglucose Positron emission tomography) scans are also being widely used to stage lymph nodal disease and distant metastasis. It also helps to assess response to neo-adjuvant therapy.(15)

4.4 TNM STAGING OF OESOPHAGEAL CANCER:

TNM staging system has been used for oesophageal malignancies, based on the 7th Edition of AJCC (American Joint Committee for Cancer) Classification(16)

T stands for primary tumor, N for nodal status and M for metastasis.

According to AJCC 7th edition:

PRIMARY TUMOR (T):

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia – all non-invasive neoplastic epithelium
T1	T1a – Tumor invades lamina propria or muscularis mucosae T1b – Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	T4a – Tumor invades resectable adjacent structures like pleura, pericardium or diaphragm T4b - Unresectable tumor invading structures like trachea, aorta or vertebra bodies

REGIONAL LYMPH NODES (N):

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodal metastasis
N1	Regional lymph nodal metastasis involving 1-2 nodes
N2	Regional lymph nodal metastasis involving 3-6 nodes
N3	Regional lymph nodal metastasis involving 7 or more nodes

DISTANT METASTASIS (M):

M0	No distant metastasis
M1	Distant metastasis

4.5 NATURAL HISTORY OF GASTRIC CANCER:

95% of gastric cancers are adenocarcinomas. Spread of gastric cancers can occur by local extension into adjacent organs, lymphatic spread, peritoneal spread and distant metastases. Tumor penetration through the serosa increases the incidence of local extension. Surgical resection is the cornerstone treatment for patients with localized gastric cancer.

4.6 CLINICAL PRESENTATION AND PREOPERATIVE EVALUATION OF GASTRIC CANCER:

Symptoms of gastric cancer are vague and non-specific which end in many patients being diagnosed with advanced disease at presentation. The constellation of symptoms vary from anorexia, fatigue, weight loss, epigastric discomfort or pain, early satiety, heart burn and indigestion. Around 4-17% may be asymptomatic.(17) There may be past history of peptic ulcer disease. Ascites, jaundice and a palpable mass at presentation point to an incurable disease.

Preoperative evaluation is carried out by endoscopy and biopsy for tissue diagnosis. Chromo endoscopy, magnification endoscopy, narrow band imaging and confocal laser endomicroscopy increase diagnostic accuracy, sensitivity and specificity. (15)

4.7 TNM STAGING OF GASTRIC CANCER:

According to the AJCC staging system,

PRIMARY TUMOR (T):

Tx	Primary tumor cannot be assessed

T0	No evidence of primary tumor
Tis	Carcinoma in situ – not invading lamina propria
T1	T1a – Tumor invades lamina propria or muscularis mucosae T1b – Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates sub-serosal connective tissue without invading visceral peritoneum or adjacent structures.
T4	T4a – Tumor invades visceral peritoneum T4b – Tumor invades adjacent structures

REGIONAL LYMPH NODES (N):

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodal metastasis
N1	Regional lymph nodal metastasis involving 1-2 nodes
N2	Regional lymph nodal metastasis involving 3-6 nodes
N3	N3a - Regional lymph nodal metastasis involving 7 -15 nodes N3b - Regional lymph nodal metastasis involving 16 or more regional nodes

DISTANT METASTASIS (M):

M0	No distant metastasis
M1	Distant metastasis

4.8 CLINICAL PRESENTATION AND PREOPERATIVE EVALUATION OF CORROSIVE INJURIES:

Corrosive ingestion, resulting in oesophageal strictures is rare in adults. The

commonest presenting feature is dysphagia. Most of these cases are managed conservatively with periodic and repeated dilatations. However, in oesophageal strictures secondary to third degree esophageal burns, surgical intervention may be required.

Preoperative preparation includes contrast studies to assess the length of the strictured segment, an upper GI endoscopy to assess the highest point of start of stricture and if possible to attempt dilatation etc. Nutritional rehabilitation, usually with feeding procedures like jejunostomies play a significant role pre-operatively.

4.9 HISTORY OF OESOPHAGEAL RESECTIONS:

Oesophagectomy remains the gold standard for curative or palliative therapy in oesophageal cancers. (10) The earliest recorded reports of esophageal surgery are descriptions of removal of foreign bodies lodged in the oesophagus in the 6th century A.D. (10) In 1877, Czerny, under the tutelage of Bilroth, performed the first cervical oesophageal resection with re-anastomosis in humans.(18) Dobromysslow(1901) reported the first intrathoracic segmental oesophageal resection with primary anastomosis.(19) All the early reports of oesophageal surgeries were associated with high morbidity and mortality, primarily due to anastomotic complications.

Torek in 1913 performed a transthoracic oesophagectomy. His patient survived 11 years, but with a plastic tube connecting the oesophagus to the stomach. Oesophageal reconstructions were deemed to cause the morbidities associated with the operations. In 1907, Roux proposed using a jejunal segment as a substitute and Kelling in 1911 proposed the use of colon as an oesophageal substitute. (19)

The first neck oesophagogastrostomy was proposed by Kirschner in 1920. Transthoracic oesophagogastrostomy was performed by Adams and Phemister in 1938. All the anastomosis were hand sewn.

The most common techniques in use today for an oesophageal resection include removal of the oesophagus with concurrent lymphadenectomy, in keeping with oncological principles.

In 1946, Ivor-Lewis performed the first successful oesophagectomy via a combined thoraco-abdominal approach. He approached the stomach through a laparotomy and the oesophagus through a right thoracotomy, effectively creating an oesophago-gastric anastomosis in the thorax.(20) A natural progression of this surgery was the McKeown's oesophagectomy. Here, following resection of the thoracic oesophagus, the tubed stomach is brought up into the neck, where it is anastomosed to the stump of the cervical oesophagus. The advantage offered by this procedure is that growths in the upper oesophagus could be resected. Furthermore, a safe, relatively easier anastomosis is performed in the neck, circumventing the dreaded complication of mediastinitis in case of an anastomotic leak.(20)

Trans-hiatal Oesophagectomy – without a thoracotomy was proposed by Orringer in 1978, primarily to avoid the physiological insult of a thoracic and abdominal incision and to avoid mediastinitis secondary to a leak in the thoracic cavity.(21)

Today, oesophagectomies are being carried out with lesser complications and better outcomes. The frontiers of oesophageal surgery are being pushed further and further by the advent of stapling devises, newer energy sources which aid in dissection and minimally invasive surgery.

4.10 SURGICAL OPTIONS FOR CORROSIVE INJURIES OF THE OESOPHAGUS:

Stricture formation remains the most common long term complication following corrosive ingestion in individuals who do not succumb to the acute complications. Around 90% of patients with third degree burns and 15 - 30% of patients with second-degree burns develop strictures.(22) Most patients with strictures are initially managed with dilatations, but many require several sittings and always carry a risk of perforation with subsequent fatal mediastinitis. Moreover, repeated dilatations are seen as procrastination in these individuals who continue to have dysphagia, aspiration and starvation. This is where surgical bypass procedures using different visceral conduits step in.

Surgeries performed for an oesophageal stricture aim at restoring intestinal continuity either via a colon pull through or a gastric pull through. A colon pull through is more commonly employed due to the possible concurrent gastric injuries caused by the corrosive ingestion. An oesophagectomy may or may not be performed as an adjunctive procedure for a colon pull through.

When considering a gastric pull through, lesser anatomical changes and a single cervical anastomosis make it an attractive option. But prior to the surgery it is mandatory to assess the gastric anatomy either by a contrast radiograph or via a Contrast Enhanced Computed Tomogram. Since lymphadenectomy is not required while performing an oesophagectomy in corrosive strictures, a thoracotomy can easily be avoided by doing a trans-hiatal dissection.(22)

When treating corrosive oesophageal strictures with surgical intervention, the question of whether or not oesophageal resection is required needs to be considered and is still a controversy.(23) The argument against leaving behind the strictured portion of the oesophagus is the risk of developing scar carcinoma in the future, the incidence of which has been reported to be around 7.2%.(24)

In cases of complete strictures, there may be a lesser incidence of malignant transformation since no further irritation occurs. In such cases an oesophageal exclusion is advocated.(25) In cases undergoing oesophageal resection, dense tissue adhesions may theoretically produce higher incidence of complications like tracheal injuries, recurrent laryngeal nerve injuries causing vocal cord palsy, poor healing at the anastomotic site etc. However, oesophageal resection along with bypass procedures has been recommended as the operation of choice in the following set of patients:

1) If the stricture is tight enough to require reconstructive surgery,

2) If there is any finding suggestive of malignancies such as long duration of the lesions of more than 30 years, or mass-like lesions on endoscopy,

3) Sudden aggravation of preexisting dysphagia.

The surgical options available are substernal oesophageal bypass surgery without oesophagectomy and oesophageal resection with replacement surgery through thoracotomy.

The conduits available for oesophageal reconstruction are the stomach, if there are no corrosive injuries, the jejunum and the colon. They are sited either in a substernal location or subcutaneously. The gastric conduit is based on the right gastro-epiploic

and right gastric arteries. The colon is reserved for cases where the stomach is deemed unsuitable due to concomitant strictures of the stomach. The right colonic conduit is based on the ascending branch of the right colic artery and the left colonic conduit is based on the left branch of the middle colic artery. In all cases of colonic conduits the assessment of vascularity is mandatory. This is performed by occluding the meso-colic vessels which have been slated for division with bull dog clamps and assessing the vascularity of the conduit prior to division. A colonic transposition changes the gastro-intestinal anatomy more than a gastric conduit. This includes delayed complications like stenosis at the anastomotic site.

In spite of advances and good outcomes in oesophageal bypass procedures, the management of proximal strictures, like those at the level of the oropharynx or cricopharynx continue to present a challenge. Any surgical interventions at this level interfere with deglutition mechanisms.(26)

4.11 COMPARISON BETWEEN HEALING IN SKIN WOUNDS AND GASTROINTESTINAL TRACT:

Effective and quick wound healing is of immense importance in gastrointestinal surgery and especially in gastrointestinal anastomosis. Failure at any point in the myriad steps of wound healing translates into prolonged hospitalization, life threatening complications, added monetary burden, and long term disabilities to the patient.(27) Hence, an overview of the factors involved in healing plays a role of paramount importance in understanding the background of anastomotic leaks.

4.12 CLASSICAL WOUND HEALING:

The classical pathway of wound healing involving the 3 phases has been classically described in skin injuries. This pathway follows a cycle of:

1. Inflammation or lag phase (2-3 days): The healing cascade kicks off with the formation of a platelet plug followed by increased vascular permeability resulting in an influx of inflammatory cells. The neutrophils, which are the first responders, rid the wound off all pathogens which triggered the inflammatory activity. This is soon followed by an influx of monocytes and tissue macrophages, which in turn secrete many growth factors.
2. Proliferative phase: This is heralded by the arrival of fibroblasts. The major portion of wound healing begins here with the various growth factors mediating the activity of the fibroblasts. The collagen in a healing wound is predominantly type III as opposed to type I collagen which is normally seen. Angiogenesis also takes place now, thereby ensuring adequate oxygenation to the healing areas, along with an influx of all the nutrients and supplementary growth factors.
3. Remodeling phase: This phase is characterized predominantly by wound contraction, reduction in the number of fibroblasts and a fall in the amount of type III collagen. (27)

4.13 HEALING IN THE GASTROINTESTINAL TRACT:

Healing in the gastrointestinal tract has the disadvantage of taking place in obscurity, where the surgeon goes by the patient's general well-being, laboratory parameters and radiological aids, to judge the healing process and thus intervene appropriately. The

process of healing in the gastrointestinal tract differs from general wound healing in a few key points.

Unlike skin, the gastrointestinal tract has four layers (mucosa, submucosa, muscularis propria, and serosa) which all contribute to healing. Halstead, proposed that the majority of strength in a GI anastomosis is provided by the submucosa.(28) There are 3 types of collagen (I, III and V) which aid in wound healing here, all of which are maximally concentrated in the submucosa. The serosa of the bowel forms a barrier, which on approximation, reduces the incidence of leaks. Absence of this layer in some portions of the gastrointestinal tract, like the oesophagus and the rectum, contributes an added risk to the anastomosis.(28)

The healing of an anastomosis in the initial few days, depends on the strength of the suture material or stapler used. During the same period, there is activation of inflammation, which produces collagenases resulting in breakdown of collagen in the region. This contributes to a weakness in the anastomosis. The maturation of the anastomosis occurs soon after as a result of formation of thick bundles of mature collagen.

4.14 VARIATIONS BETWEEN SKIN AND GASTROINTESTINAL HEALING:

Healing in the skin and gastrointestinal tract, although occurring along the same general principles, deviates in certain other ways. The rate of wound healing in a GI anastomosis is more rapid than in skin. It occurs in weeks as opposed to months. However, this rapidity in healing is partially contributed by the serosal layer which forms a physical barrier, the absence of which weakens anastomotic integrity.(28)

Other factors which adversely affect the gastrointestinal anastomosis are the bioburden of aerobic and anaerobic organisms, the shear stresses over the wound and the precarious vascularity. The predominant determinant among these is vascularity, which gets downregulated secondary to hypotension causing hypo perfusion of the anastomosis. (19) Yet another significant factor threatening an anastomosis is the increased collagenase activity which further acts to weaken the healing wound.

4.15 FACTORS INFLUENCING ANASTOMOTIC HEALING:

A gastrointestinal anastomosis is the weakest at the beginning of the wound healing process due to the collagenase activity. At 48 hours the strength of the anastomosis weakens by 40% due to this. Once proliferation and remodeling begin, the anastomosis starts gaining strength. (27) During this period the anastomosis is at risk of giving way since the bursting pressure is at its lowest. (Bursting pressure is defined as the maximal intraluminal pressure which will result in the anastomosis giving way.)(27).

There are two major factors which determine the successful healing of any wound, including a gastrointestinal anastomosis. These are commonly categorized as local factors and systemic factors. In cases, where an oesophageal anastomosis is involved there are a third set of "inherent factors" that add a unique dimension which plays a vital role in the healing of the anastomosis and plays a role in the anastomotic leaks, which can be devastating or even fatal, in an oesophagectomy.

4.15.1 SYSTEMIC FACTORS:

The major systemic factors influencing healing are:

1. Nutrition
2. Sepsis
3. Immuno-compromise secondary to diseases, medication etc.
4. Fluid depletion and shock
5. Poor glycemic control and other metabolic disorders
6. Alcoholism
7. Compromised liver disease
8. Chemotherapy

4.15.2 LOCAL FACTORS:

The local factors involved in healing are:

1. Local infection
2. Mechanical factors like poor apposition, excessive mobility etc.
3. Foreign bodies
4. Size, location and type of wound
5. Technical errors
6. Gastric compression
7. Compromised vascularity
8. Conduit ischemia
9. Tension across the anastomotic junction
10. Distal obstruction

4.16 COMPLICATIONS OF AN OESOPHAGEAL ANASTOMOSIS:

The complications following an oesophagectomy and oesophageal anastomosis can be broadly divided into those related to the anastomosis and those, which are not.

The **non-anastomotic complications** include pulmonary infections, pleural effusion, thoracic duct injury with chyle leak and chylothorax, cardiac arrhythmias, recurrent laryngeal nerve injury, postoperative venous thromboembolism etc. Out of these complications, pulmonary complications form the major burden and can be as high as 44% to 46% incidentally.(29)

Anastomosis related complications form a major bulk of post-operative morbidity and even mortality.(30) They have significantly decreased over decades but still form a major burden. This decrease in incidence is attributed to a better knowledge of anatomy, refined anastomotic techniques and modern perioperative care.(30)

Anastomosis related complications include bleeding with hematoma formation, anastomotic leaks, and wound infections secondary to a leak etc., in the short term followed by strictures or disease recurrence in the long term.(31) Out of all these, leaks form the bulk of the most serious and lethal acute complication of an oesophageal anastomosis.

4.17 OESOPHAGEAL ANASTOMOTIC LEAKS:

4.17.1 DEFINITION:

The incidence of anastomotic leaks following oesophageal cancer resection can range as high as 17% and is accompanied by a mortality of up to 60%.(32) A literature review of the definition of an anastomotic leak spans a wide spectrum from clinical

definitions to those confirmed by radiological imaging or at re-operation. This lack of a consensus in definition skews the available data on incidence of anastomotic leaks. Some of the common definitions are reviewed here:

Young Lee (1994):

An **anastomotic leak** is defined as having (1) necrosis, (2) a major leak with clinical manifestations requiring surgical repair, (3) a major leak which spontaneously healed, and (4) a minor leak (a "radiological leak").(33)

Urschel (1995):

A **post oesophagectomy anastomotic leak** is a radiologically or clinically apparent oesophago-gastrostomy anastomotic dehiscence.(32)

Ihabb I. El Hajj (2014):

Leaks were defined as postoperative dehiscence of the peri-anastomotic region.(34)

Surgical Infection Study Group (1991):(35)

LEAK	DEFINITION
Radiological	No clinical signs
Clinical minor	-Local inflammation at the neck wound -X-ray showing contained leak -Fever, leukocytosis, elevated CRP
Clinical major	-Severe disruption on endoscopy -Sepsis
Conduit necrosis	-Endoscopic confirmation

As a consensus, an anastomotic leak includes a hematoma or seroma at the neck wound, septicemia, peritonitis, peri-anastomotic collection, local inflammation, evacuation of air or saliva from the wound, mediastinitis, abscess, empyema and pneumothorax.(30)

4.17.2 RISK FACTORS FOR AN OESPHAGEAL ANASTOMTOIC LEAK:

The systemic and local factors influencing healing of an anastomosis along with a brief overview of the factors inherent to an oesophageal anastomosis have already been reviewed earlier. Out of the systemic factors involved hypertension and elevated creatinine (>0.85 mg/dl) were found to be independent risk factors for a cervical anastomotic leak. (28) This was attributed to poor tissue micro perfusion.

The factors influencing an oesophageal anastomosis will be reviewed in detail here.

The properties exclusively inherent to an oesophageal anastomosis include(32):

1. Absence of serosa
2. Extra-peritoneal nature of the structure
3. Longitudinal muscle coat which holds sutures poorly
4. Technically awkward suturing
5. Difficult reconstructive techniques requiring extensive mobilization of conduits.

Furthermore, the factors which can possibly influence an oesophageal anastomosis are

1. The tumor histology, stage and location of the tumor,
2. The organ used as an oesophageal conduit and intra-operative factors,
3. The technique and location of anastomosis (cervical or intrathoracic),

4. Single Vs. double layer suturing,
5. Manual suturing Vs. mechanical stapling,
6. Distance between the anastomosis line and the tumor,
7. Microscopic involvement of surgical resection margins,
8. Neo-adjuvant radiotherapy or chemotherapy.(36)

1. THE TUMOR HISTOLOGY, STAGE AND LOCATION OF THE TUMOR:

   It has been reported that factors pertaining to the tumor like the histology, size and location do not adversely influence the leak rates. However, the tumor differentiation could increase the incidence of a leak, with poorly differentiated tumors having a higher leak rate.(36)

2. THE ORGAN USED AS AN OESOPHAGEAL CONDUIT AND INTRA-OPERATIVE FACTORS:

   Intra-operative factors which can affect an anastomosis adversely are intra-operative hypotension which has a negative effect on the tissue perfusion and oxygenation. The conduits commonly used as oesophageal substitutes are the stomach, colon and jejunum, in that order of preference. The stomach conduit is based on the right gastroepiploic vessels. The significance of this anatomical fact, is that approximately 60% of the gastric tube is supplied by this vessel, the cranial 20% is supplied by minute connections between right and left gastroepiploic vessels and the most cranial 20% is vascularized through a dense submucosal and microvascular network. Since the oesophago-gastric anastomosis is constructed at the proximal 20% of the gastric fundus, any trauma in the form of application of suction devices, traction sutures to

facilitate the gastric pull-up maneuver etc. can predispose to anastomotic leaks.(37) A tension free anastomosis, especially if the proximal portion with doubtful vascularity is resected, can be ensured by performing a Kocher's maneuver and pulling up the gastric tube.(38)

The colon has a more consistent vascularity and in high volume centers the outcomes between gastric conduits and colonic conduits in terms of complications are almost identical. The jejunal conduit has the most precarious vascularity of the three conduits. This is attributed to the technical difficulty involved in creating a sufficiently long tube which will not kink or compromise the vascularity. (37)

Gastric distension, postoperatively can predispose to a leak and is circumvented by doing a pyloroplasty or pyloromyotomy to facilitate easier drainage.(39) But the drawback of this procedure in the long risk is the possibility of duodeno-gastric reflux causing delayed anastomotic stricture and Barrett's metaplasia.

3. <u>THE TECHNIQUE AND LOCATION OF ANASTOMOSIS (CERVICAL OR INTRATHORACIC):</u>

The technique of oesophageal resection, trans-hiatal versus transthoracic and the incidence of anastomotic leaks in each, continues to be under debate. 2 randomized controls were performed by Goldminc et al(40) and Chu et al(41) which failed to prove any differences in outcomes. This was followed by an analysis carried out by Papenfuss et al. They concluded that serious morbidity remains clinically significant in both groups. But the group undergoing trans-hiatal oesophagectomies had a significantly higher superficial wound infection rate while the group undergoing trans-

thoracic oesophagectomies required more perioperative blood transfusions and higher re-operation rates.(42)

4. SINGLE VS. DOUBLE LAYER

   The construction of an oesophageal anastomosis can be single layered or double layered. The single layered technique for bowel anastomosis was proposed by Halsted in the 19th century(43). This was countered by Czerny in 1880 who proposed double layered suturing.(44). This century old debate was laid to rest by a Cochrane review article in 2012 which did not demonstrate any appreciable differences in outcomes between these two groups.(45)

5. MANUAL SUTURING VS. MECHANICAL STAPLING:

   The progressive fall in complications following an oesophagectomy has been attributed to advances in operative techniques and perioperative care. One of the newer advances is the use of circular staplers to perform the oesophageal anastomosis. The stapling device is said to be less traumatic, consumes less operating time and has an easier learning curve.(46) A prospective randomized control trial conducted by Liu et al.(46) cited that staplers were superior to hand-sewn anastomosis in terms of preventing anastomotic leaks but on follow up, were associated with a two-fold increase in stricture rates. A meta-analysis by Wang et al. in 2015 concluded stating that there were no difference in complication rates between the two techniques. But they also summarized that staplers were more cost effective and associated with shorter hospital stays. (47) The higher rate of stricture formation is caused by a lack of accurate mucosa-to-mucosa apposition, tissue necrosis beyond the staple line and the

non-absorbable staplers which prevent the lumen from dilating more than the original size. All these factors are negated in a hand sewn anastomosis.(47)

6. COMPARISON OF LEAKS IN CERVICAL AND THORACIC ANASTOMOSIS:

   The leak rates between cervical and thoracic anastomosis gain significance as the morbidity and mortality rates between the two vary. Cervical leaks are associated with less morbidity and mortality as compared to intra-thoracic leaks. The higher incidence of cervical leaks has been explained by a multitude of reasons like tension across the anastomosis due to longer length of the conduit, extrinsic compression, and the non-mesothelial environment of the neck. (48) The relative safety of a cervical leak lies in the propensity for early detection, feasibility of bedside drainage procedures etc. Recent studies fail to demonstrate a definitive higher incidence but have proven that cervical anastomotic leaks are associated with lower mortality rates than thoracic leaks.(49)

7. MICROSCOPIC INVOLVEMENT OF SURGICAL RESECTION MARGINS:

   Oesophageal cancer has a well-recognized tendency to spread intra-murally as well as have multiple separate lesions at the same time. This phenomenon contributes to the microscopic involvement of the resection margins. Though, theoretically this can predispose to higher incidence of anastomotic leaks, the issue remains controversial. There are studies which support the hypothesis like those by Urschel et al. (48) and there are articles from Simon et al (50) which refute it. Hence, the additional risk of an involved margin remains debatable.

8. NEO-ADJUVANT RADIOTHERAPY OR CHEMOTHERAPY:

Oesophageal cancers are now as a rule tackled by multimodality treatment, even though surgery remains the curative option. Hence, the effect of neo-adjuvant therapy, chemotherapy, radiotherapy or both, on surgical outcomes needs inspection. Wolfard et al. in 2011 reported a higher incidence of post-operative anastomotic leaks following NACRT.(51) This was followed up by a meta-analysis by an European study group in 2014 which failed to demonstrate an increase in anastomotic leaks after NACRT.(52) This had been further borne out by a study published in 2015 by Hamai et al.(53)

4.17.3 CLINICAL FEATURES OF AN OEOSPHAGEAL ANASTOMOTIC LEAK:

The clinical presentation of an anastomotic leak following an oesophagectomy spans a wide spectrum ranging from asymptomatic, clinically silent leaks detected by routine radiology to those which present in sepsis.(48) This was decided primarily by the following factors:

1. Viability of the conduit used in reconstruction
2. Site of the leak – cervical Vs. thoracic
3. Degree of containment of leak by surrounding tissues
4. Time of detection and intervention.

In 1995, Urschel presented a landmark paper which classified the severity of leaks according to the clinical presentation.(48)

CATEGORY OF LEAK	TIME	ETIOLOGY	CLINICAL PRESENTATION
EARLY FULMINANT	<48 hours	Gross technical errors Gastric necrosis	Septic shock Foul chest drain output
CLINICALLY APPARENT THORACIC LEAK	2-7 days	Multifactorial	Sepsis GI contents in chest tube Pleural collections on radiography
CLINICALLY APPARENT CERVICAL LEAK	2-10 days	Multifactorial	Fever Inflamed neck wound Drainage via neck drain or neck incision
CLINICALLY SILENT	Routine radiograph on day 7	Multifactorial	Small, asymptomatic, clinically silent, contained leak

4.17.4 SYSTEMIC FEATURES OF AN OESOPHAGEAL ANASTOMOTIC LEAK:

The clinical features which would suggest a leak are:

- Tachycardia (heart rate > 100 beats per minute),
- Fever (body temperature > 38°C),
- Tachypnea (high respiratory rate), > 20 breaths per minute
- Leukocytosis (> 12 × 103/ml)

4.17.5 LOCAL FEATURES:

CERVICAL ANASTOMOTIC LEAKS: Localized swelling, erythema, tenderness, subcutaneous emphysema, purulent discharge and halitosis or oral feeds expelled from the neck wound are features suggestive of a cervical anastomotic leak.(54)

THORACIC ANASTOMOTIC LEAKS: Pleural effusion, shortness of breath, chest pain, atrial dysrhythmias, bilious drainage from the chest tube, hydro-pneumothorax, vomiting and subcutaneous emphysema over the chest wall or neck may point at an intra-thoracic anastomotic leak.(55)

ABDOMINAL LEAKS: In total gastrectomies, the oesophago-jejunal anastomosis is sited in the peritoneal cavity. These leaks, along with the systemic features can present with peritonitis and expulsion of intestinal contents in the drain.

4.17.6 CLINICAL PREDICTORS OF SEVERITY OF AN OESOPHAGEAL ANASTOMOTIC LEAK:

The severity of an oesophageal leak can be predicted by certain factors as below: (56)

1. Time of manifestation: The earlier a leak occurs, it's more likely to be secondary to technical errors or conduit necrosis. In such a scenario, lack of time for the surrounding tissues to contain the leak results in higher morbidity.

2. Leaks with clinical manifestation: This again is attributed to lack of surrounding tissue reaction, which fails to contain the leak.

3. Leaks requiring surgical intervention: In individuals where operative intervention is performed for an anastomotic leak, mortality risks increase. This is evidently in direct proportion to the severity and florid nature of the leak.

4. Conduit necrosis: Gastric necrosis has been reported as the only unequivocal predictor of mortality secondary to esophageal leaks. This complication is associated with a large defect that leaks freely into the exterior in cases of cervical anastomosis. The same leak in an intra-thoracic anastomosis can be lethal. In worst case scenarios, the foregut continuity may be lost secondary to conduit necrosis.(56)

5. Delayed diagnosis: Failure to detect a leak or failure to deal aggressively with it after diagnosis, have been proven to have poorer outcomes.

4.18 HISTORY OF UPPER GI CONTRAST STUDIES:

The concept of visualizing the upper gastrointestinal tract by using radio-opaque materials was heralded by Dr. Cannon who initiated the development of upper GI contrast study series by his studies on a goose. He observed the passage of bismuth sub nitrate impregnated grains through the gullet of a goose using Roentgen rays.(57) The first radio-opaque foreign body to be detected within the oesophagus was an iron staple in the year 1898 by Bliss.(58). Following these papers, radiological

evaluation of the gastrointestinal tract grew from the basics to the sophisticated modalities available today.

Different preparations and formulations of barium sulfate were then investigated through the ages for their efficacy in opacifying the gastrointestinal tract and offering improved delineation of mucosal details also.(59) As a natural progression of events Brombart et al described the use of barium sulfate solution to study oesophageal anatomy. This was translated to the use of the solution to identify oesophageal tears or perforations and further studies went on to assess the effects of the chemical on the mediastinum and the peritoneal cavity.(60) Himmelman in 1933 pronounced barium sulfate to be harmful to the peritoneal cavity. This was further proved by Thomas et al who proved the pathology behind the inflammation and the formation of barium granulomas with adhesions as the final outcomes. This was followed by papers which advocated the use of laparotomy and peritoneal lavage if barium extravasated into the peritoneal cavity following swallow studies or enemas.

Christofordis, Reich and Andrews et al individually published results to prove that unlike the peritoneal cavity, barium was less harmful to the mediastinum and lungs than aqueous contrast media.(60) This was attributed to the transient mechanical blockage caused by barium on aspiration. Whereas, when hypertonic water soluble contrast media enter the lungs or mediastinum, it is more distressing than barium, with aspiration resulting in pulmonary edema.(61)

Vessal et al, in 1975, published his work on assessing the usefulness of aqueous contrast media like Gastrografin as compared to contrast media like Barium sulfate. He aimed at assessing the efficacy of either material as well as the deleterious

effects of both in case of mediastinal or peritoneal extravasation in cats. His recommendations advocated the use of aqueous contrast media to delineate distal oesophageal tears followed by the use of barium in cases of a negative study for confirmation.(60)

All the above proved the superiority of barium sulfate over Gastrografin in detecting anastomotic leaks. It also laid down the guidelines that barium was safe to assess mediastinal leaks and Gastrografin to assess peritoneal leaks.

4.19 TESTING THE INTEGRITY OF AN OESOPHAGEAL ANASTOMOSIS:

After the establishment of contrast radiography to detect oesophageal tears and perforations it was a natural transition to use the same modality to assess integrity of oesophageal anastomosis after an oesophagectomy. This gained a foothold since the most dreaded complication of an oesophagectomy, which determined the outcome of the surgery, was an anastomotic leak. The recommendations were that if there was no evidence of aspiration, water based contrast media (sensitivity-40%) was used as the first line of radiography. If no leaks were detected, this was followed up with a barium contrast (sensitivity-60%) studies for confirmation.(61)

The poor sensitivity of aqueous contrast media, risk of iodine induced anaphylaxis and pulmonary edema secondary to aspiration prompted the preference of barium swallows as the investigation of choice in assessing post-operative anastomotic leaks.(61)(62) This formed the basis of recommending a routine post-operative upper gastrointestinal contrast study after an oesophagectomy. This practice

was gradually questioned after the advent of newer and safer ways of predicting leaks along with studies showing poor sensitivity of swallow studies.(63)

4.20 CHANGE IN TREND OF UPPER GI CONTRAST STUDIES:

One of the earliest studies questioning the use of Gastrografin in assessing cervical anastomotic leaks was published from AIIMS, India by A.K.Goel et al.(64) in 1995. They advocated the use of test feeds with saline followed by milk and using clinical predictors to diagnose anastomotic leaks rather than doing a Gastrografin swallow. They also stated that minor leaks missed by the above technique did not adversely affect the patients.(64)

A paper brought out by Tirnaksiz et al. (2005)(2) assessed the sensitivity, specificity and positive predictive value of Gastrografin swallow in detecting leaks of cervical and intra-thoracic anastomosis. In cervical anastomosis, the sensitivity was 43.7 % and specificity was 95.4 %. In intra-thoracic anastomosis, the sensitivity was 30% and specificity was 94.5%. This study went on to show that the high specificity of Gastrografin swallow in detecting leaks, after an Ivor-Lewis oesophagectomy came at the price of low sensitivity.

The study proposed discontinuation of the practice of a routine upper gastrointestinal contrast study for the following reasons:

1. The risk of aspiration and pulmonary edema associated with Gastrografin swallow.

2. A negative study on the 7th post-operative day did not exclude the possibility of a delayed leak and in fact caused a complacence and delay in intervention with associated increase in morbidity.

This was followed up with a study by Tonouchi et al.(2006)(65) who also pronounced that contrast studies had a sensitivity of only 50% and did not recommend repeat studies as confirmation. They went on to advocate the use of Contrast Enhanced Computed Tomograms to rule out strongly suspected leaks.

Daniel et al in 2012(4) went on to consolidate the thought process of giving up routine contrast studies with Gastrografin to assess anastomotic leaks.

Christopher et al. published a best evidence topic paper in 2015. They analyzed 5 major publications by Goel et al, Solomon et al, Tirnaskiz et al, Boone et al and Cooke et al. The bottom line of their meta-analysis was that the low sensitivity and positive predictive values of routinely used upper gastrointestinal contrast studies precluded their use as a mandatory study in patients with no clinical features to suggest an anastomotic leak following a cervical anastomosis.(66)

4.21 ALTERNATIVES TO PREDICTING ANASTOMOTIC LEAKS:

Since an oesophageal anastomotic leak still poses a challenge both in terms of detection and treatment, selective imaging with oral contrast study or alternative methods for evaluating the integrity of an oesophageal anastomosis may be practiced. The overall consensus, however lies in careful monitoring of clinical signs that suggest a leak. All other modalities are taken as adjuncts to aid in the diagnosis when a leak is suspected.

Some of the techniques described by various teams are:

1. Contrast Enhanced Computed Tomography
2. Test feeding
3. Electrolyte gated method
4. Endoscopy

1. Contrast Enhanced Computed Tomography:

The path to using CECT for detecting intra-thoracic anastomotic leaks was laid by Heiken et al(67) in 1984. This was followed by other studies assessing the usefulness and superiority of CECT over routine barium oesophagograms. The advantage offered by a CT scan over an oesophagogram is attributed to its ability to pick up indirect signs of a leak. These could be loculated or free fluid or gas in the mediastinum as in cases of sealed off leaks. However, this higher sensitivity is offset by a lower specificity as the above findings may be secondary to post-operative changes. Another added advantage is the ease of doing a CECT as compared to a fluoroscopic examination in very ill or less mobile patients. (68)Doing a CT study with oral contrast increases specificity in cases of ongoing leaks but offers no benefit in sealed leaks.(69) In addition, residual barium from an oesophagogram interferes with the interpretation of CT images due to scatter.

Strauss et al in 2010, stated that a CECT done on post-operative day 7 had greater sensitivity and specificity in detecting anastomotic leaks following an Ivor-Lewis than a contrast swallow.(70) This was further backed up by Kim et al who also suggested that the size of the leak, and extent of contrast extravasation could be pointers to the severity of the leak.(71)

2. Test feeding:

There have also been descriptions of using methylene blue to detect intra-thoracic leaks in patients with drains in situ to detect leaks, especially in clinically ill patients(72)(73).

Test feeds with water have been described, especially in detection of cervical anastomosis.(64) Boone et al in 2008, conducted a study to compare the outcomes of using water as a test feed while observing the cervical anastomosis and doing a routine oeosphagogram. They proved the superiority of water test feeds but confined their results to a cervical anastomosis only.(3)

3. Electrolyte gated method:

This novel technique was proposed by Dearmond et al in 2013(74). It has been named as the electrolyte-gated leak detection (EGLD). This test has been based on detection of electrical changes induced by electrolyte extravasation from a leak site. The electrolyte used was normal saline. This is still in the experimental phase but so far has shown promise with high sensitivity as well as specificity. The use of an inert substance like saline adds to its potential as a safe and effective alternative to oesophagograms.(74)

4. Endoscopy:

Endoscopic examination, accompanied by air insufflation, has been viewed skeptically because of the theoretical danger of anastomotic dehiscence, post oesophagectomy. Maish et al, heralded a change in this line of thinking in 2005, when they assessed the integrity of an oesophageal anastomosis in terms of graft ischemia, graft loss and anastomotic leak. The advantage quoted by their study was that,

following an endoscopic evaluation of the anastomosis, in clinically unwell patients, other causes like pneumonia, wound infection or abscess, line sepsis, pulmonary embolism, liver failure etc. were sought for and addressed earlier.(75)

The added advantage is that an endoscopic evaluation allows a measure of freedom to intervene, in the form of stents if an early leak is detected. Furthermore, an endoscopic assessment is the only way to assess the viability of the conduit adjacent to the leak. Thus the information gained by an endoscopy can be used to tailor treatment to the individual.(76)

In patients with discordant radiological findings, endoscopic evaluation is deemed the confirmatory test.(68)

Fujiwara et al have gone on to advocate day 1 endoscopy to look for Mucosal Color Change (MCC) as an early predictor of loss of anastomotic integrity and poor healing of the anastomosis.(77)

4.22 PRESENT KNOWLEDGE AND JUSTIFICATION OF THE STUDY:

Thus, multiple studies have stated the drawbacks and pitfalls of doing a routine contrast swallow oesophagogram post operatively. Additionally, the day of doing the study, amount of contrast required, positioning of the patient etc. are as yet debated factors.

Moreover, the low sensitivity and specificity of these studies when weighed against the potential dangers of aspiration, missed anastomotic leaks, delayed anastomotic leaks, cost of the procedure, prolongation of hospitalization etc., raise questions that need justification.

Most of the studies have been retrospective in nature and been conducted in developed countries. In India, where the healthcare system is burdened with low doctor patient ratios, inadequate health benefit packages, the use of a redundant imaging modality is not advisable. Hence, this study is being performed with the aim of phasing out a practice that offers no real time benefits but could potentially reduce length of stay in the hospital and the financial burden.

If this study shows no added morbidity in patients who are not routinely subjected to an upper GI contrast swallow, then the routine use of this practice can be abandoned in those without clinical indicators of a leak. Furthermore, a protocol could be drawn up to compare the different indices and their sensitivity in predicting leaks. In those with a high suspicion of leaks, more sensitive and specific modalities can be employed.

5. MATERIALS AND METHODS

The Institutional Review Board of Christian Medical College, Vellore, reviewed this study in October 2013 and approved the trial in February 2014. The trial was then registered with the Clinical Trial Registry of India (REF/2014/04/006881). The study was conducted from March 2014 to June 2015.

This was a Randomized Control Trial carried out among patients in a single General Surgical unit. The main factor looked at for inclusion was the presence of an oesophageal anastomosis. Thus, the **inclusion criteria** were:

1. All patients undergoing an oesophageal anastomosis (hand sewn or stapled)
2. McKeown's Oesophagectomy
3. Ivor-Lewis Oesophagectomy
4. Total Gastrectomy
5. Colon bypass procedures or stomach pull through for corrosive strictures.
6. Patients undergoing an oesophageal anastomosis and other surgeries concurrently (Ex: Cholecystectomy, Splenectomy etc.)

The **exclusion criteria** were:

1. Patients refusing to participate in the study.
2. Pregnant ladies.

There was no deviation from the standard pre-operative evaluation and preparation. The surgery plans were made after Multi-Disciplinary Tumor board meetings. The patients fitting the inclusion criteria were explained about the proposed study plan and informed written consent was obtained. Post-operatively the patients were randomized to two groups as follows:

GROUP A:

All the patients from the Group A underwent a routine upper GI contrast study between post-operative days 7 to 9 in keeping with the current practice. However, if clinically indicated (Ex: To assess the extent of leak, to plan further course of management etc.) the patient may undergo a Contrast Enhanced Computed Tomogram scan. The decision as to whether to go ahead with a Barium or Gastrografin swallow or to withhold it in favor of higher, more sensitive imaging like a Contrast Enhanced Computed Tomogram scan was taken by the operating surgeon and the team. This was included as part of an intention to treat during the final analysis.

GROUP B:

Patients from Group B did not undergo a routine upper GI contrast study. Instead, they were serially monitored for the below mentioned signs of an anastomotic leak. If there was a clinical suspicion of a leak, they underwent a radiological imaging as per the discretion of the treating surgeon, which was most likely to be a Contrast Enhanced Computed Tomogram. The clinical features which were suggestive of a leak are:

- Tachycardia (Heart rate > 100 beats per minute),
- Fever (Body temperature > 38°c),
- Tachypnea (high respiratory rate), with greater than 20 breaths per minute
- Local or generalized peritoneal reaction during physical examination
- Leukocytosis (> 12×10^3/ml)
- Wound infection/discharge in case of neck anastomosis.

*All the above were strictly and serially monitored in these patients and presence of any 2 out of these was used as reliable clinical indicators of an anastomotic leak.

INTERVENTION AND COMPARATOR AGENT:

Outcomes of performing an upper GI contrast study between post-operative day 5 to day 7 versus no upper GI contrast study esophagogram were assessed.

METHOD OF RANDOMIZATION:

Randomization was performed with the help of computer generated randomization through numbers. The codes were issued in a sealed envelope. The group to which each patient was randomized to was conveyed to the operating team post-operatively.

METHOD OF ALLOCATION CONCEALMENT:

The allocation of patients was concealed pre-operatively. After the surgery, sealed envelopes with the randomization code were opened by the principal investigator and the randomization informed to the team.

BLINDING AND MASKING:

There was no masking or blinding performed during the study.

SAMPLE SIZE CALCULATION:

Sample size calculation was performed after going through other similar studies performed world-wide. For more accuracy, preliminary work was carried out by

assessing the retrospective data from the institution in the last 2 years, prior to starting the study. Although routine upper GI contrast study was being performed for all oesophageal anastomosis, some patients had been managed without a routine contrast study. Since this trial was proposed to assess the need for change in current practice, data on patients who had undergone an oesophageal anastomosis over the last 2 years, from General Surgery Unit 3 was analyzed based on available In-Patient records.

The outcomes considered were:

- Delay in starting normal diet.
- Prolonged hospital stay.

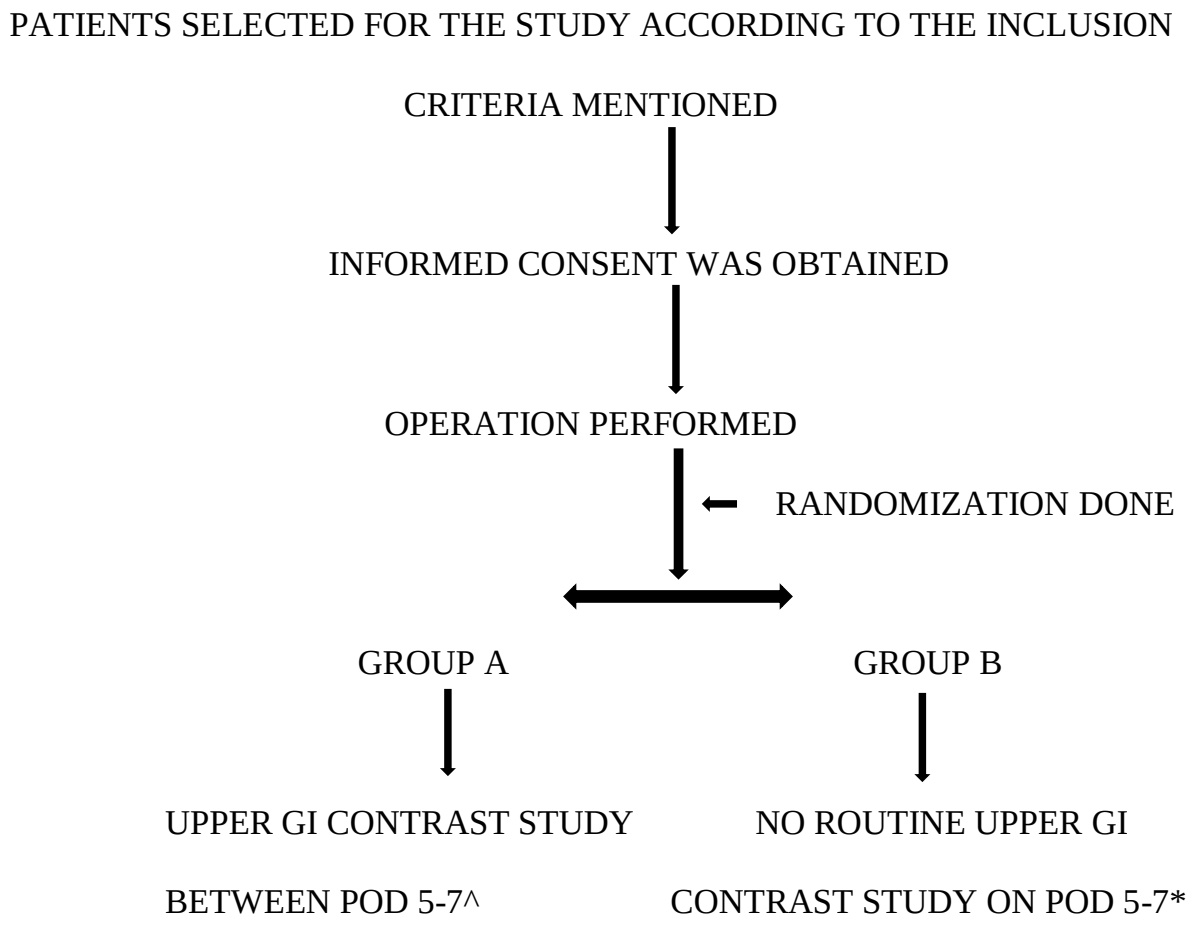
17% and 30% was the prevalence in the two conditions.

The difference is considered as 10% and the average as 23 %. 77% is the complement of 23% i.e. 100-23 = 77.

Using a formula n= 4PQ/ D*D

Sample size = 75 in each arm.

DIAGRAMMATIC ALGORITHM OF THE STUDY:



In both the groups, serial monitoring of clinical parameters like temperature, pulse rate, blood pressure, respiratory rate, signs of peritonitis or wound infection was carried out. The patients were also monitored for any major or minor morbidities that may occur.

Complications were classified according to the Clavien-Dindo grading system as follows:

Grade I:	Fever controlled with antipyretics only Severe pain controlled with analgesics Wound infection/discharge opened at bedside Paralytic ileus
Grade II:	Wound infection/sepsis requiring antibiotic therapy Chest infection managed with antibiotic therapy Abdominal infection managed with antibiotic therapy Post-operative blood transfusions Total parenteral nutrition Anastomotic leak managed with antibiotics only
Grade III:	Anastomotic leak with endoscopic intervention needed Anastomotic leak with radiological intervention needed Anastomotic leak with surgical intervention needed Other complications requiring

	endoscopic intervention / radiological intervention / surgical intervention
Grade IIIA	If not requiring general anesthesia
Grade IIIB	If requiring general anesthesia
Grade IVA	Respiratory failure only or Renal failure
Grade IVB	Respiratory failure Renal failure Septic shock Multi organ dysfunction
Grade V:	Death of the patient

The duration of post-operative day was calculated in both groups. The day of operation was considered as post-operative day 1. The day of starting oral feeds, liquids followed by solids was recorded in both groups. The other data collected included demographic variables, risk factors like comorbid illness, nutritional status, preoperative chemotherapy or radiation therapy, stage of the disease etc. Intra-operative factors like details of anaesthesia and blood transfusions, surgical details including technique, type and site of anastomosis etc. were noted. Post-operative details included the course in the hospital in terms of general wellbeing, clinical variables, laboratory parameters, duration of hospital stay etc.

For the patients randomized to Group A, who were slotted for a mandatory upper GI contrast study, a study was fixed according to the location of the anastomosis. The details of the randomization were conveyed to the operating team. In this group the day of starting liquids was determined by the patient's clinical course and the day of starting a solid food was determined by a normal contrast study on POD 7-9.

The patients who had systemic features to suggest a leak clinically, like fever or tachycardia were assessed diligently. Depending on the clinical picture and general condition of the patient a Contrast Enhanced Computed Tomogram was usually opted for by the operating team. The rationale being that, apart from confirming a leak, the extent of a peri-anastomotic collection and feasibility of radiological intervention for the same could be assessed. It had been decided at the start of the study to include these set of patients as part of an intention to treat analysis.

In patient with features of Systemic Inflammatory response Syndrome, apart from considering an anastomotic leak, other causes like urinary tract infection, pneumonia etc. were also concurrently evaluated.

After the upper GI contrast study was performed, the films were reviewed by the treating surgeons as well as officially reported by the radiologists.

PROTOCOL VARIATIONS CONSIDERED:

a. Interim analyses: If unable to complete target size, the data collected till then will be analyzed for significance.

b. For withdrawal of participants: The participants are allowed to withdraw at their discretion. If randomization has been done the numbers will be returned to the table.

c. For premature stopping of trial: The reasons for the same will be analyzed and published.

6. RESULTS AND ANALYSIS

A randomized control trial was performed in the General Surgery Unit III, Christian Medical College, Vellore, from March 2014 to June 2015. In this study a total of 40 patient were recruited. The data collected during the course of this study was analyzed with STATA 13.1 software. The statistical tests used were mainly the Independent sample t-test, Pearson $\chi 2$ statistic and Fisher's exact test. A P-value of < 0.05 was considered statistically significant.

Prior to starting the trial, a retrospective analysis was performed to assess the standard operating protocol employed after an oesophagectomy. Two years of data was analyzed. Of the 118 patients operated in this time period, 25% had been managed post operatively without undergoing a mandatory upper GI contrast study. Out of this 25%, one-third had anastomotic leaks which were detected clinically or radiologically (CT scan being the most common modality), without a routine upper GI contrast study being performed. The remaining two-thirds had an uneventful post-operative period and were discharged on a normal diet. There was no morbidity or mortality in this group, where a routine contrast study was not performed. This data was also considered while calculating the sample size. Thus, the standard operating protocol existing in the unit meant that majority of patients underwent routine upper GI contrast studies after an oesophageal anastomosis – most commonly on the 7^{th} post-operative day.

A total of 40 patients consented to be included into the study. They were randomized post-operatively into 2 groups wherein group A underwent a mandatory contrast study between the 7^{th} and 9^{th} post-operative days. The patients in group B were monitored strictly with clinical parameters to detect leaks early.

6.1 DEMOGRAPHIC PROFILE BETWEEN GROUPS:

	GROUP A	GROUP B
AGE: (Mean / SD)	48.1 (+/-14.29)	50.3 (+/- 12.3)
SEX: Males: 30 (75%) Females:10(25%)	20(90.91 %) 2(9.09%)	10(55.56%) 8(44.44%)
HISTOPATHOLOGY: Adenocarcinoma – 40% Squamous cell carcinoma – 37.50% Corrosive strictures – 15% Leiomyoma – 2.50% GIST – 5%	 9(40.41%) 7(31.82%) 4(18.18%) 1(4.55%) 1(4.55%)	 7(38.89%) 8(44.44%) 2(11.11%) 0(0%) 1(5.56%)
LOCATION OF TUMOR/STRICTURE Upper one-third of the oesophagus – 5% Middle one-third of the oesophagus – 37.50% Lower one-third of the oesophagus – 15% Gastro-esophageal junction – 20% Fundus of the stomach – 7.50% Body of the stomach – 15%	 0(0%) 8(36.36%) 3(13.64%) 8(36.36%) 1(4.55%) 2(9.09%)	 2(11.11%) 7(38.89%) 3(16.67%) 0(0%) 2(11.11%) 4(22.22%)
OPERATIONS PERFORMED: Ivor-Lewis oesophagectomies – 17.50 % McKeown's oesophagectomy – 40% Total gastrectomies – 30% Colon/gastric pull through – 12.50%	 1(5.56%) 9(50.00%) 6(33.33%) 2(11.11%)	 6(27.27%) 7(31.82%) 6(27.27%) 3(13.64%)

ANASTOMOTIC LEAKS (Radiological and clinically detected)	3	2
ANASTOMOTIC LEAK DETECTED RADIOLOGICALLY	1	0
DAY OF STARTING LIQUIDS (Mean / SD)	7.36(+/- 3.33)	6.52(+/-1.84)
DAY OF STARTING SOLIDS (Mean / SD)	9.72(+/-3.34)	7.58(+/-3.35)
LENGTH OF HOSPITAL STAY IN DAYS (Mean / SD)	13.63(+/- 3.78)	12.83(+/-3.71)
MORTALITY	0	0

6.2 GENDER DISTRIBUTION:

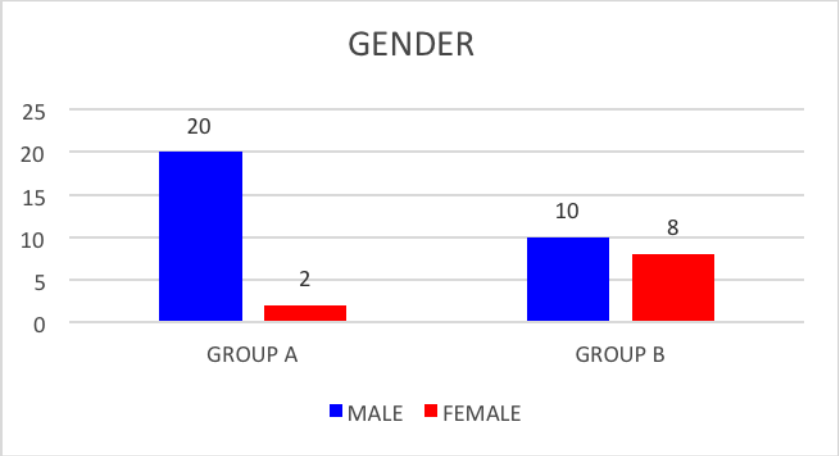


FIGURE 1

Of the 40 patients recruited, there were 20 males in group A and 10 males in group B. There were 2 females in Group A and 8 females in group B. There was a definite male preponderance in the study population with 75% of the participants being male. This was in keeping with world literature that shows a predominant male population in oesophageal and gastric malignancies.

6.3 SMOKERS vs. NON SMOKERS:

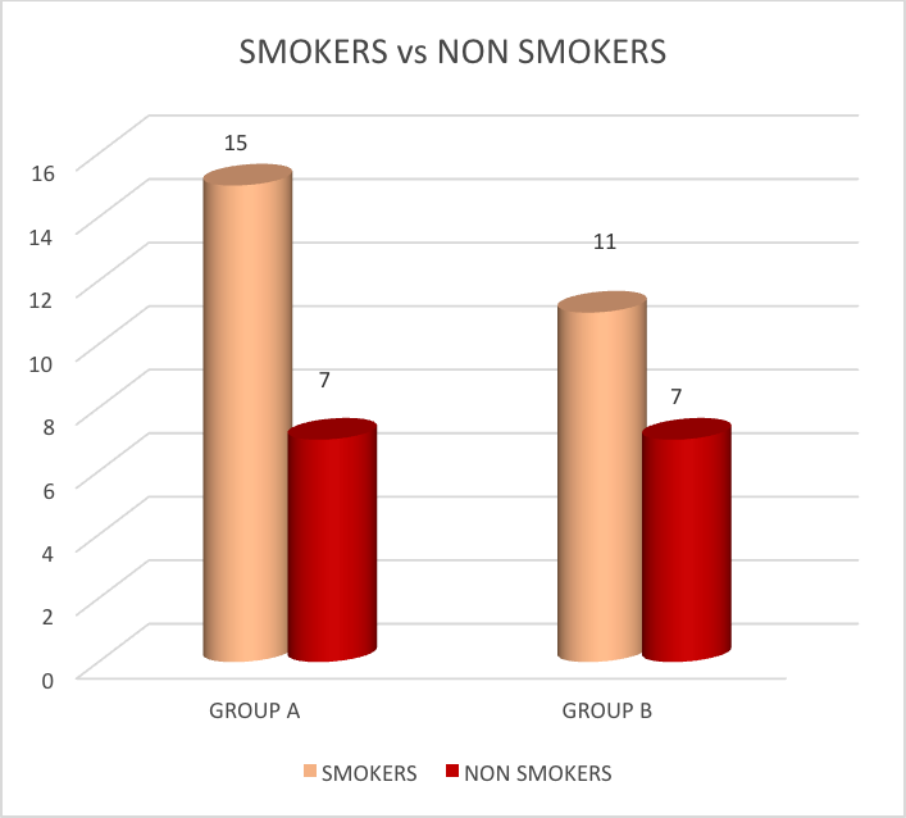


FIGURE 2

There were 26 smokers and 14 non-smokers in Group A and B respectively. This constituted 65% and 35%. This difference was in parallel to the sex distribution with males forming the bulk of the smoking population.

6.4 ALCOHOL CONSUMERS Vs NON CONSUMERS:

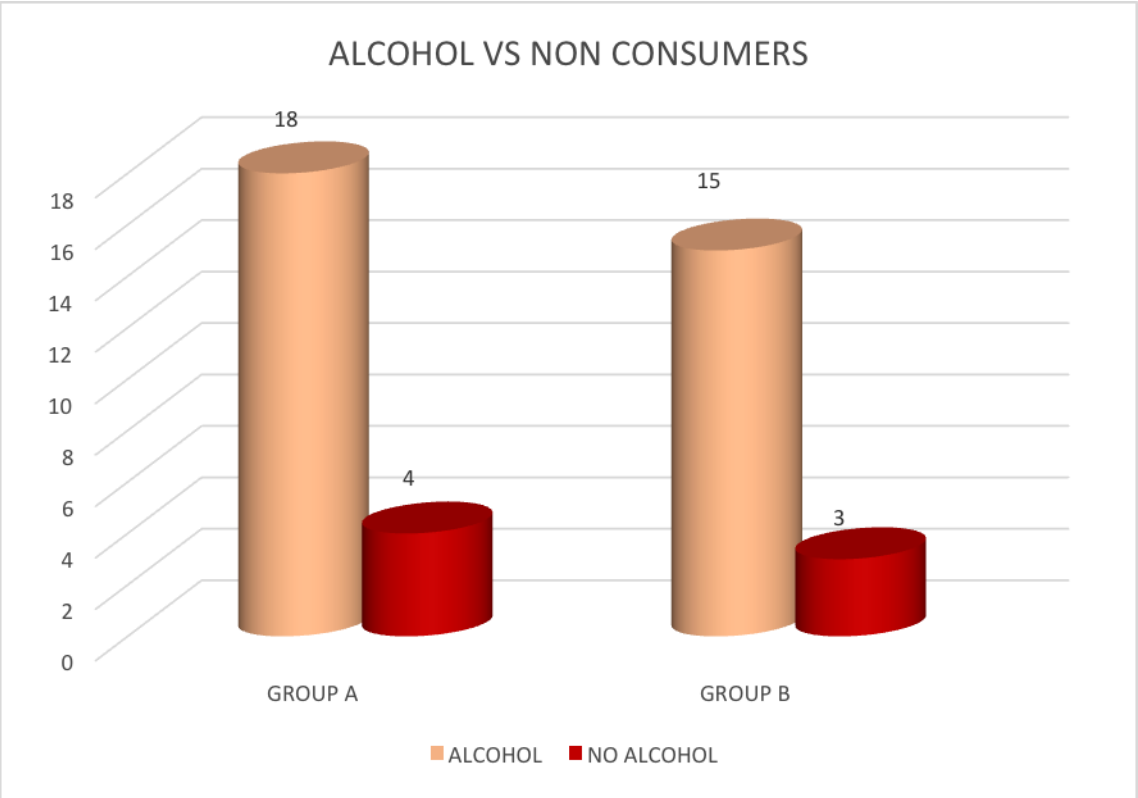


FIGURE 3

Alcohol consumption among the study population was 82.50 % in group A and 17.50% in group B with 33 consumers and 7 consumers respectively. This again reflected the sex distribution.

6.5 DIAGNOSIS AND INDICATIONS FOR OESOPHAGECTOMY:

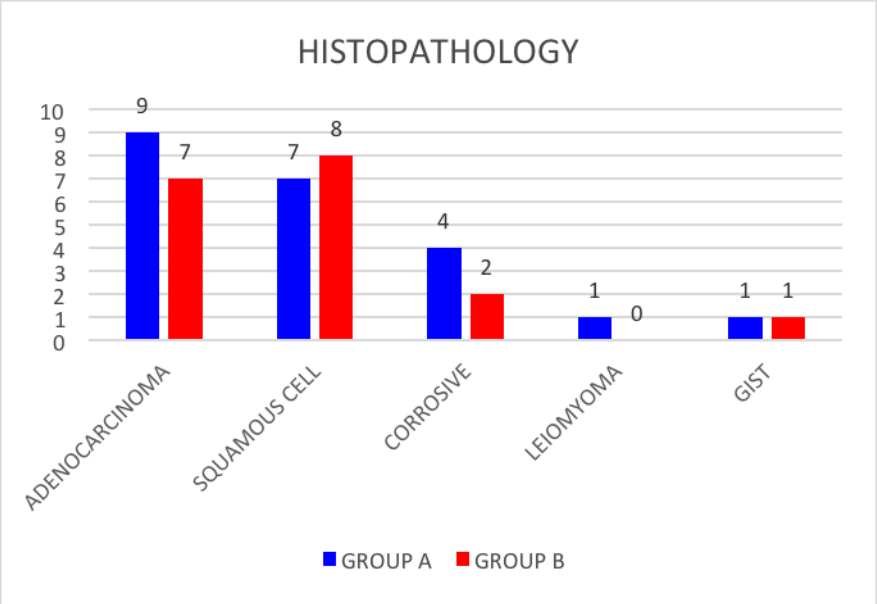


FIGURE 4

The indications for an oesophagectomy included oesophageal malignancies, gastro-oesophageal junction malignancies, proximal gastric cancer and corrosive oesophageal strictures. The histopathological variations among lesions is distributed as follows:

1) Adenocarcinoma – 40%
2) Squamous cell carcinoma – 37.50%
3) Corrosive strictures – 15%
4) Leiomyoma – 2.50%
5) GIST – 5%

6.6 LOCATION OF THE LESION:

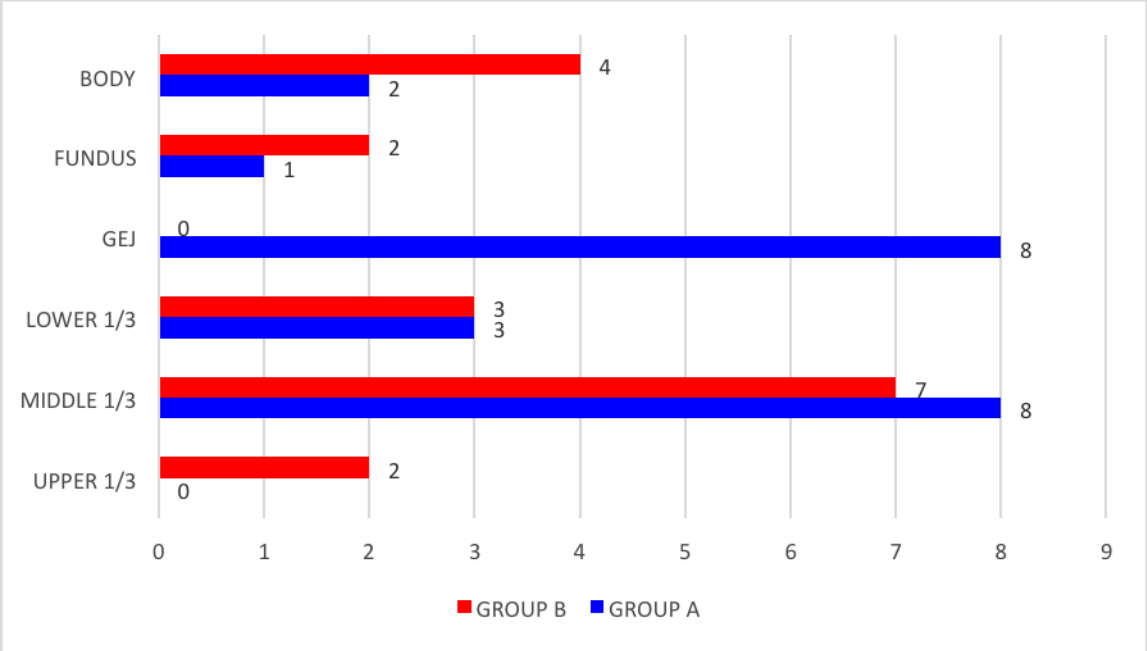


FIGURE 5

1) Upper one-third of the oesophagus – 5%
2) Middle one-third of the oesophagus – 37.50%
3) Lower one-third of the oesophagus – 15%
4) Gastro-esophageal junction – 20%
5) Fundus of the stomach – 7.50%
6) Body of the stomach – 15%

6.7 OPERATIONS PERFORMED:

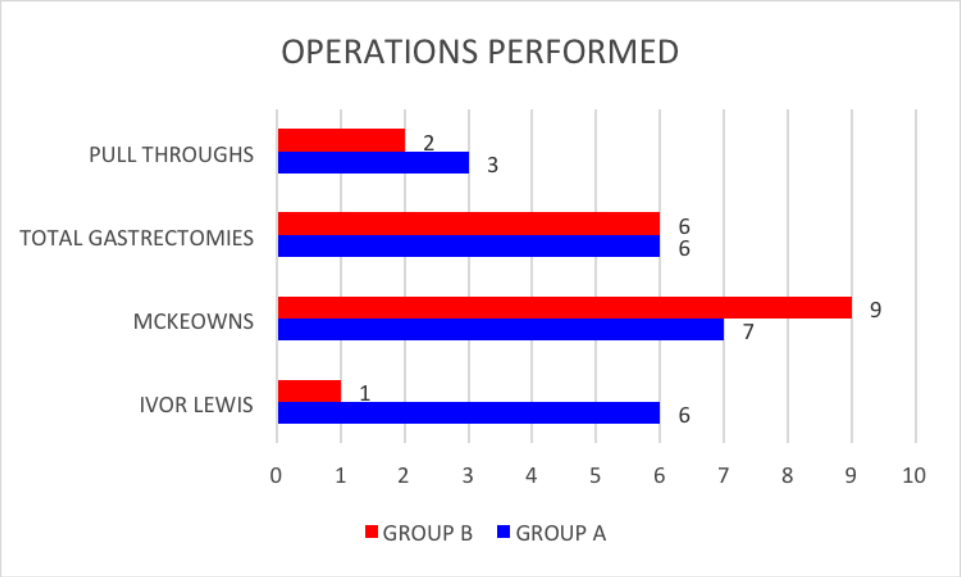


FIGURE 6

The surgical procedures performed included Ivor-Lewis oesophagectomies, McKeown's oesophagectomies, total gastrectomies and bypass procedures for strictures.

The incidence of procedures was:

1) Ivor-Lewis oesophagectomies – 17.50 %
2) McKeown's oesophagectomy – 40%
3) Total gastrectomies – 30%
4) Colon/gastric pull through – 12.50%

The rates of these procedures among the study population reflected the trend in location of tumors and strictures.

6.8 ANASTOMOTIC LEAKS:

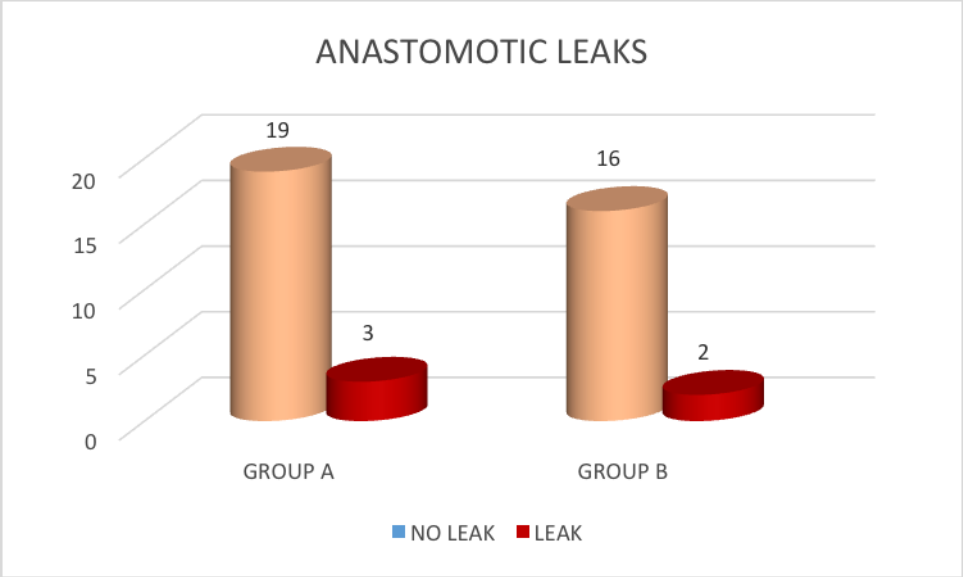


FIGURE 7

The overall leak rate among the study population – detected clinically or by imaging was 12.50%. 3 patients in Group A and 2 in Group B had an anastomotic leak.

The leak rates between groups were comparable. However in group A out of the 3 leaks only 1 leak was detected by the routine barium swallow. This was a total gastrectomy with an intra-abdominal leak. Both the cervical anastomotic leaks were missed and were detected on test feeds.

Out of the 2 cervical leaks in Group B, both were clinically detected.

6.9 SITE OF ANASTOMOSIS AND INCIDENCE OF ASSOCIATED LEAKS:

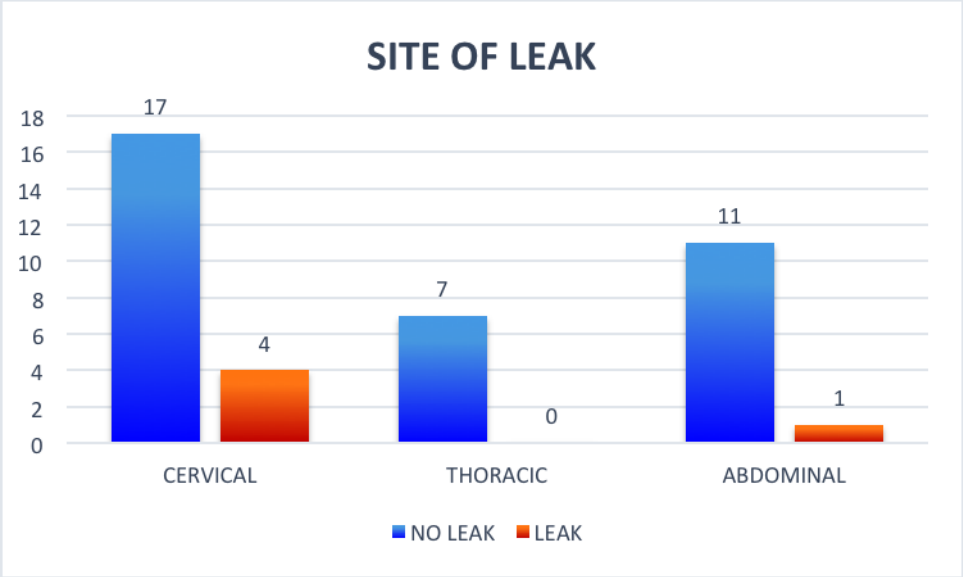


FIGURE 8

There were a total of 5 leaks in the study population (n = 5/40; 12.50%). There were 4 cervical anastomotic leaks, no intra-thoracic leaks and 1 intra-abdominal leak. The higher incidence of cervical leaks was probably an outcome of the increased incidence of McKeown's oesophagectomies in the study population. However, on analyzing these numbers with the Chi square test, a P value of 0.365 was derived, showing that the site of anastomosis did not confer an added risk. Thus, the apparently high incidence of cervical anastomotic leaks was not statistically significant.

6.10 ANASTOMOTIC TECHNIQUE AND INCIDENCE OF LEAKS:

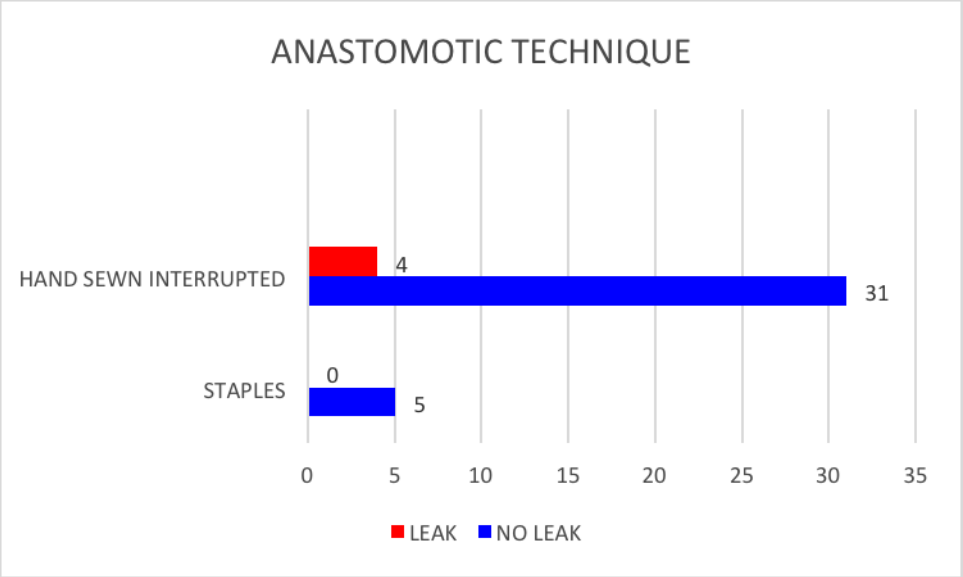


FIGURE 9

The two commonly favored anastomotic techniques were hand sewn interrupted sutures and mechanical staples. The preference was as follows:

1. Hand sewn interrupted (n = 35/40; 87.50%)
2. Staples (n = 5/40; 12.50%)

The leak rates between the 2 techniques were analyzed with Chi square test. The P value was 0.738 which was not statistically significant.

6 SENSITIVITY AND SPECIFICITY OF UPPER GI CONTRAST STUDIES:

SENSITIVITY	13.60%
SPECIFICITY	88.60%
POSITIVE PREDICTIVE VALUE	60.00%
NEGATIVE PREDICTIVE VALUE	45.70%

The sensitivity and specificity of upper GI contrast studies were assessed in comparison to clinically or CECT detected leaks. It was found that the test had a significantly low sensitivity but fairly good specificity. In routine practice it was more helpful to rule out a leak than to detect anastomotic leaks.

6.12 DAY OF STARTING LIQUIDS ORALLY:

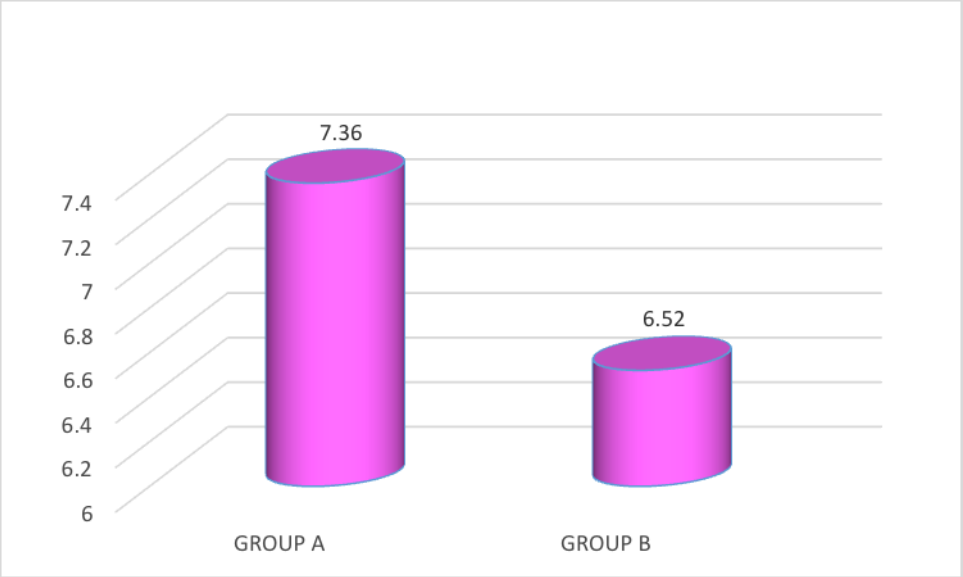


FIGURE 10

Out of the 40 patients recruited, 1 could not be started on oral feeds due to persistent aspiration. On an average the patients in Group A started taking liquids on the 7th post-operative day and those in Group B started on the 6th post-operative day. There was no statistical difference in this outcome between the groups (P value – 0.359).

6.13 DAY OF STARTING SOLIDS:

FIGURE 11

As part of the study protocol and in keeping with existing practice, the patients in Group A started taking solid diet after a normal upper GI contrast study. Hence, on an average, members in Group A were started on solids on the 9th post-operative day while those who were in Group B started taking a normal diet on the 7th post-operative day. Chi square test produced a P value of 0.0553 which revealed a probable statistically significant difference in between groups.

6.14 LENGTH OF HOSPITAL STAY:

FIGURE 12

The length of hospital stay after the operation differed by a day between the two groups. On an average the patients in group A stayed a total of 13.6 days while those in Group B stayed for 12.8 days. However, this difference was not statistically significant (P value – 0.505).

6.15 COMPLICATION RATES:

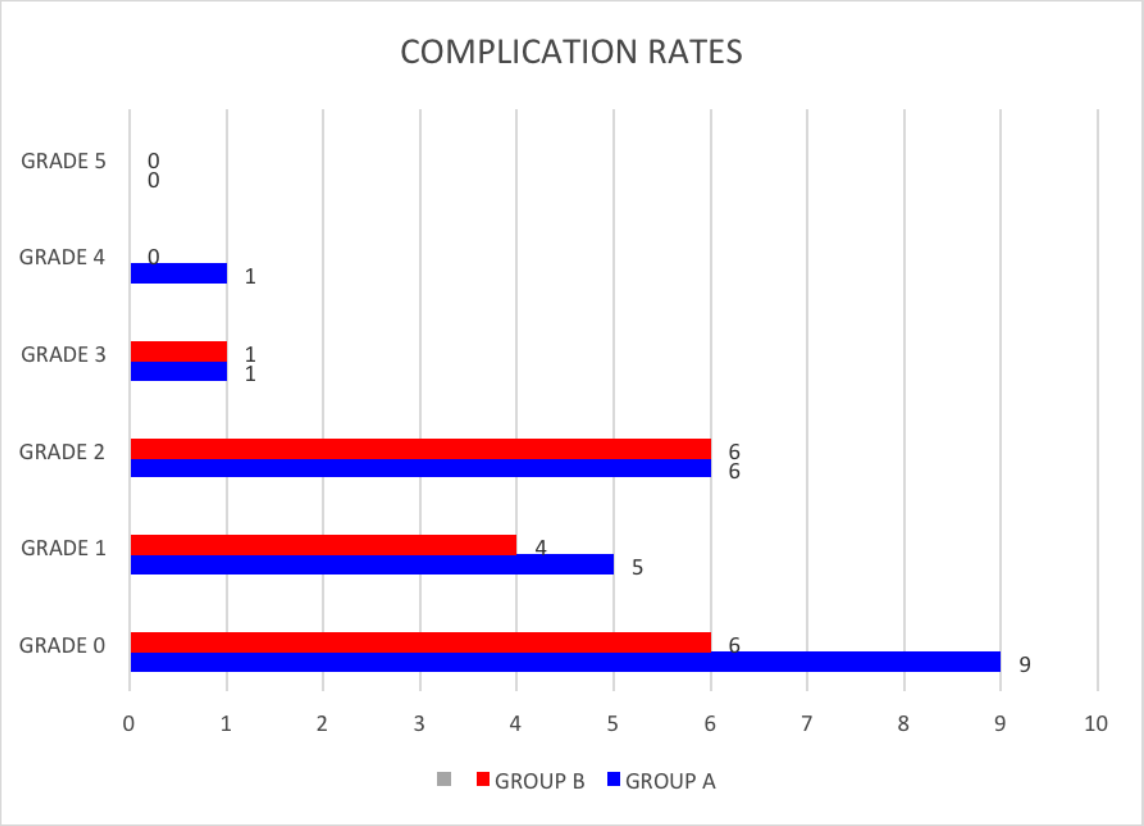


FIGURE 13

The complications occurring among patients in both groups were classified according to the Clavien-Dindo grading system. Out of the 40 patients, who were part of the study, 15(38.46%) had an uneventful post-operative period. 9(23.08%) had Grade 1, 12(30.77%) had Grade 2 and 2(5.13%) had Grade 3 complications. Only 1(2.56%) patient had a Grade 4 complication. There were no mortalities in the study population. Statistical analysis of the complication rates did not reveal any significant change in the incidence of complications between groups. (P value – 0.896)

6.16 COMPARISON OF RE-ADMISSION, RE-INTUBATION AND RE-OPERATION RATES:

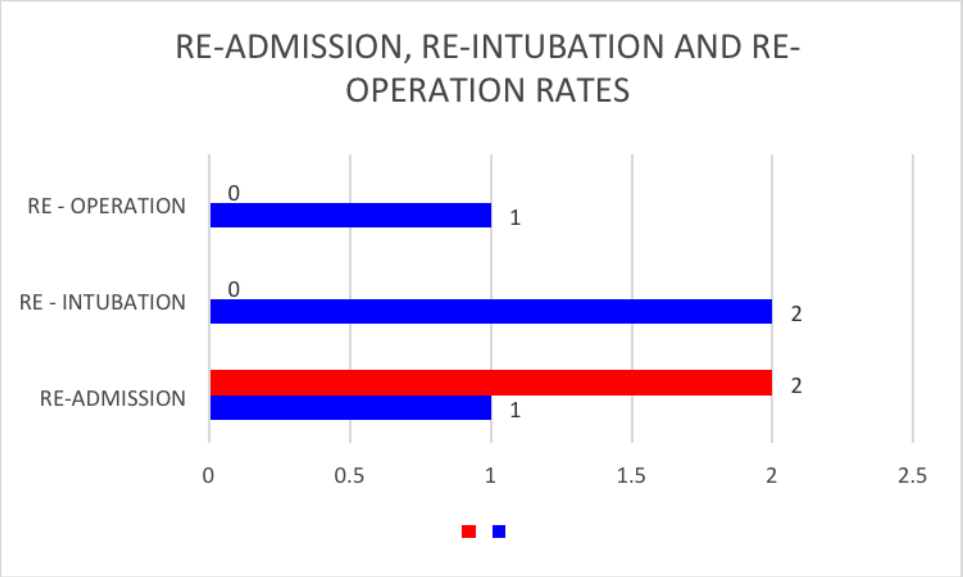


FIGURE 14

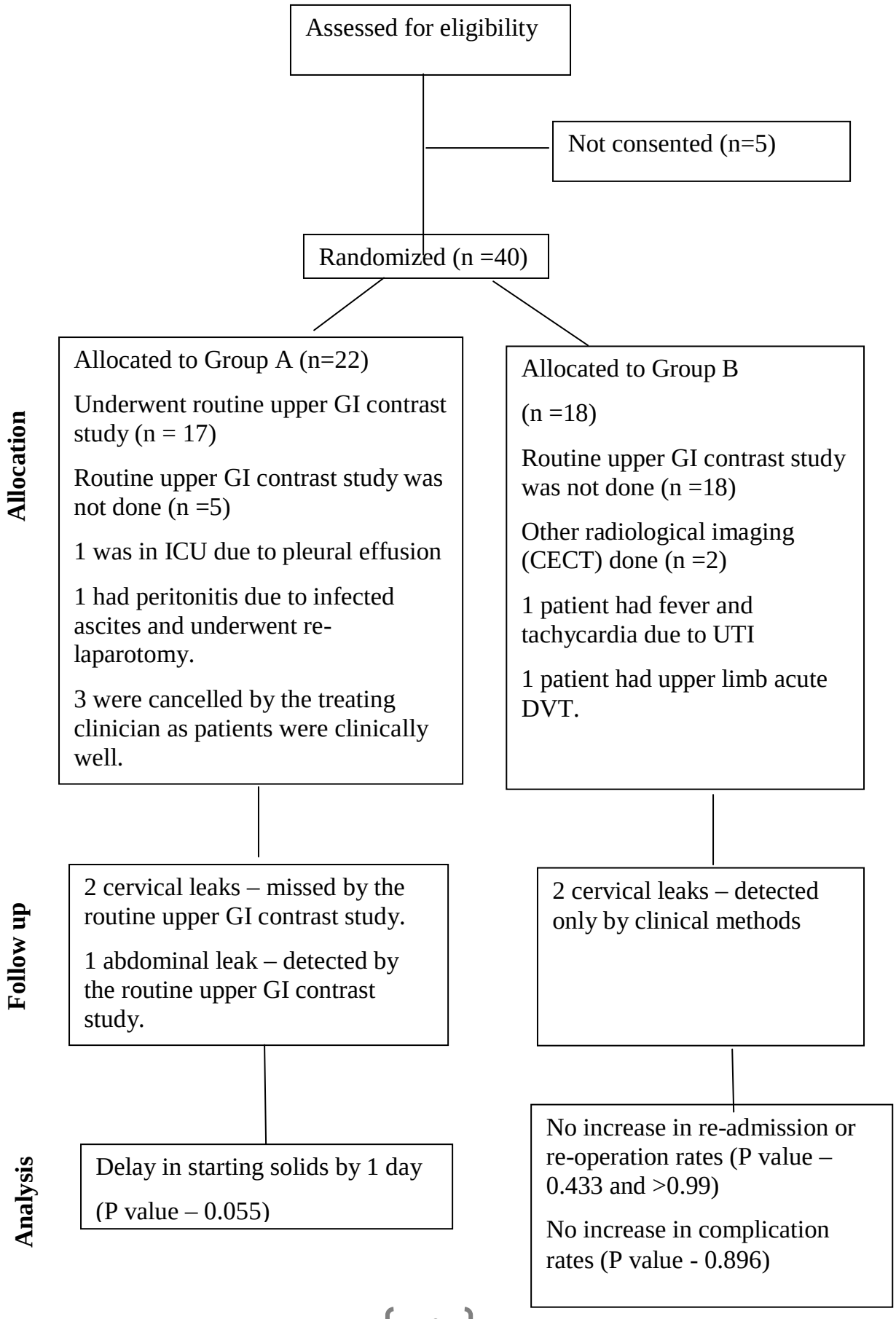
In Group A, 1 patient was re-admitted for conservative management of a wound dehiscence, which occurred following discharge. He had had a normal contrast study. In Group B, 2 patients were re-admitted. 1 was detected to have deep vein thrombosis following a central venous access catheter insertion and another was admitted for urinary tract infection. In Group A 2 patients were re-intubated. One for unexplained deterioration with hypoxia, hypotension and tachycardia and the second for an infected ascites, requiring peritoneal lavage. There were no patients who required re-intubation or re-operation in Group B. Statistically, the P values for comparing re-admission, re-intubation and re-operation rates were 0.433, 0.492 and >0.99.

6.17 SYNOPSIS OF OUTCOMES AND STATISTICAL SIGNIFICANCE:

VARIABLE	VALUES	SIGNIFICANT OR NOT
Leaks according to the technique of anastomosis	.738	Not significant
Leaks according to the location of the anastomosis	.549	Not significant
Difference in date of starting liquids	.359	Not significant
Difference in date of starting solids	.055	Probably significant
Difference in length of hospital stay	.505	Not significant
Difference in complication rates	.896	Not significant
Difference in re-admission rates	.433	Not significant
Difference in re-intubation rates	.492	Not significant
Difference in re-operation rates	>0.99	Not significant

7. DISCUSSION

7.1 CONSORT CHART:



Five patients in Group A failed to undergo the scheduled upper GI contrast study. One patient had fever, tachycardia and peritonitis. He underwent a CECT of the abdomen, for a suspected leak which showed an infected ascites. He underwent a laparotomy and peritoneal lavage. Following the lavage, he improved and was discharged well. The 2nd patient failed to undergo the scheduled study because he had persistent, unexplained tachycardia post operatively. On further evaluation he was found to have developed pleural effusion which was the reason for the tachycardia.

In group A, the other 3 patients failed to undergo the scheduled routine upper GI contrast study since the operating team felt it was unwarranted.

One patient in Group A had unexplained hypotension and desaturation on the 10th post-operative day for which he was re-intubated and started on inotropic supports. He had undergone a routine barium swallow on the 7th post-operative day which was normal. However, in view of his deterioration, a missed anastomotic leak was suspected and he was subjected to a Contrast Enhanced Computed Tomogram. The study failed to yield any useful results due to the residual barium coating the oesophagus which caused intense scatter. This has already been quoted as a drawback of doing routine upper GI contrast studies. The patient was offered supportive care and recovered fully after 72 hours and was subsequently discharged on a normal diet orally.

17 patients were randomized to Group B and hence did not undergo a routine upper GI contrast study. In this group 2 patients had anastomotic leaks at the cervical region which were picked up clinically and managed conservatively. Two other patients underwent Contrast Enhanced Computed Tomograms for suspected anastomotic leaks

when they developed fever and tachycardia. One patient was later proven to have urinary tract infection and the second patient had acute Deep Vein Thrombosis of the upper limb secondary to a central venous access catheter placement. She underwent a re-operation for the same (Clavien – Dindo Grade IV complication).

The non-anastomotic complications among the group members included pneumonia, urinary tract infections, acute cholecystitis etc.

Five patients out of 40 had anastomotic leaks which were detected either during the upper GI contrast study or clinically. There were 4 cervical anastomotic leaks (2 in Group A and 2 in Group B), 1 intra-abdominal anastomotic leak and no intra-thoracic anastomotic leaks. All the cervical anastomotic leaks in Group A were missed by the contrast study but were detected clinically. There were no added adverse effects secondary to the cervical leaks. The patient with an intra-abdominal leak was suspected to have a leak, based on the high, bilious drain output, prior to the study. This was confirmed by the upper GI contrast study which revealed extravasation at the oesophago-jejunal anastomosis (Radiograph in Annexure 1). She was managed conservatively and was discharged well. There were 2 anastomotic leaks in group B and both were cervical leaks which were picked up clinically without the need for a contrast study.

7.2 COMPARISON OF STUDY DATA WITH WORLD LITERATURE:

The anastomotic leak rate in this study was 12.50%. The literature available on the incidence of anastomotic leaks spans a wide range. Urchel et al reported the incidence

of anastomotic leak to be 17% in their series(48) and Bardini et al reported it to be as high as 53%(37). This wide disparity and range of incidence in anastomotic leaks is due to a lack of consensus for the definition of an anastomotic leaks. Most papers which we reviewed, relied on contrast studies to define leaks. The drawback to this is that most centers around the world now rely on clinical parameters to detect leaks since clinically occult leaks are usually of no grave consequence.(37) The average leak rate was around 15 – 20%(79) and our leak rates were within recommended norms.

Barium sulfate is an inorganic compound. It is a white crystalline solid that is odorless and insoluble in water. It is used as a radiocontrast agent for imaging the GI tract. Although barium is a heavy metal, and its water-soluble compounds are often highly toxic, the low solubility of barium sulfate protects the patient from absorbing harmful amounts of the metal. Barium sulfate is also readily removed from the body. However, while performing an upper GI contrast study to look for anastomotic leaks after an oesophagectomy, the risk of aspiration needs to be considered. Barium was less harmful to the mediastinum and lungs than aqueous contrast media if aspirated (69). In patients with an intra-abdominal anastomosis, barium sulfate can cause chemical peritonitis. Hence, the alternative in these patients is Gastrografin (Diatrizoate Meglumine) which is an iodinated radiocontrast agent. Gastrografin is contraindicated in patients at risk of aspiration as it can result in pulmonary edema due to its hypertonic nature.

In this study patients with cervical and thoracic anastomosis underwent thin barium studies while those with abdominal anastomosis underwent a Gastrografin study.

In Group A, where a routine contrast study was performed 2 patients had complications due to the study. 1 patient developed profound cough and the study was prolonged. Another patient has aspiration into the trachea-bronchial tree, though he recovered uneventfully following the same (Radiograph in Annexure 2). There were no major adverse effects. Incidentally, these patients expressed a strong dislike to the taste and texture of the solution and stated it to be an unpleasant experience. The majority of the patients who had refused to participate in the study had undergone a pre-operative barium swallow and hence cited the unpleasant taste to be a reason for refusing consent.

As part of the study, the upper GI contrast study for these patients was funded by the Institution. Otherwise an additional cost of Rs.1250 would have been borne by the patients. Thereby avoiding a routine contrast study will save the above mentioned cost to the patient.

There were 2 cervical anastomotic leaks in patients randomized to Group B. They were both detected clinically and managed conservatively. Thus, no anastomosis related complications were missed in Group B. Two other patients were suspected to have anastomotic leaks due to fever and tachycardia, but were diagnosed to have UTI and DVT respectively. They were subjected to CECT scans as per the study protocol.

The sensitivity and specificity of upper GI contrast studies in our series was 13.60% and 88.60% respectively with a confidence interval of 95%. Around the world, studies by different authors have claimed sensitivity ranging from 47% to 85%(68) and specificity ranging from 73 – 97% (68).

Tirnaksiz et al(2) and Tonouchi et al(65) assessed the usefulness of Gastrografin / Barium swallow as a screening procedure for anastomotic leaks in 2005 and 2007 respectively. Tirnaksiz et al found the test to have a sensitivity of 40.4% and specificity of 97%. As per their data the false positive rate was 5.2% and false negative rate was 59.5%. The outcome of both trials was to use Gastrografin or barium swallows as a screening test following total gastrectomy with great caution, I view of the low sensitivity of these modalities. This data is compared with our study below.

	CMC STUDY	TIRNAKSIZ ET AL
SENSITIVITY	13.60%	40.4 %
SPECIFICITY	88.60 %	97.0%
POSITIVE PREDICTIVE VALUE	60.00%	43.5 %
NEGATIVE PREDICTIVE VALUE	45.70 %	94.1%

The day of starting oral feeds following an oesophageal anastomosis has significance since gastric distension following the operation and poor anastomotic wound maturity have been cited as reasons for late leaks(after 7 days).(37)(48)

However, recent studies by Cooke et al have shown that by the 7^{th} – 10^{th} post-operative day most patients are well enough to take a solid diet and be discharged. The drawbacks of delay in start of feeds can add to prolonged hospital stay and the accompanying morbidities.(54) Our study showed a statistically significant delay of 1

day in starting solid diet in patients who were subjected to a routine upper GI contrast study.

Goel et al, in 1995, questioned the practice of doing a routine Gastrografin swallow to assess cervical oesophageal anastomotic integrity. They performed a prospective trial among 25 patients, where test feeds with water detected 3 anastomotic leaks including 1 missed by the subsequent Gastrografin swallow. They proposed test feeding with graded feeds starting from water to be a better option, than routine upper GI contrast studies with low sensitivity(64). This was further emphasized by Boone et al, in 2008, who advocated that the routine practice of doing a Gastrografin swallow be abandoned in favor of water test feeds. (81) In our study this was true for 4 out of 4 leaks where there was extravasation of test feeds from the neck. Out of these 2 patients had a false negative Barium swallow oeosphagogram.

Griffin and Lamb et al in 2001, studied the efficacy between upper GI contrast study and flexible upper GI endoscopy in detecting mediastinal leaks. During the course of their study 6 patients with normal contrast studies developed endoscopy proven leaks.(6) In our study population there were no intra-thoracic anastomotic leaks detected clinically or on radiological imaging. Another study was performed by Griffin et al in 2004 to assess usefulness of barium swallow to assess an oesophago jejunal anastomosis following a total gastrectomy. They published that 2 out of 8 leaks proven by endoscopy were missed by the barium swallow.(6)

There were no studies that compared the length of hospital stay between groups.

Maxime Nguyen et al in 2014, carried out a prospective trial to assess the usefulness of upper GI barium swallows in detecting occult anastomotic leaks.(7) This study was

carried out among 221 patients and it was concluded with the recommendation that a contrast oesphagogram was not an ideal screening modality to detect anastomotic leaks. They further advised the use of this test in a targeted fashion for patients with suspected leaks and systemic features of the same.

The latest work in this field has been a Best Evidence Topic paper published in 2015 by Christopher M. Jones et al. They reviewed the articles by Cooke, Boone, Tirnaksiz and Goel et al. They said that the pros and cons of doing a routine upper GI contrast study after an oesophageal anastomosis precluded its use as a routine screening test.(66) They also commented that there were no adverse outcomes seen in those not undergoing the study. In our study the comparison of complications between groups did not show a statistical difference.

This study reiterates the fact that doing a routine upper GI study confers no added clinical benefit. Instead, it delayed the initiation of solids by one day. Furthermore, there was no increase in complication rates by foregoing the study in clinically well patients.

8. LIMITATIONS OF THE STUDY

- The calculated sample size was not attained. Hence, the results from the study should be applied to the general population with caution and judiciousness.

- There were more cervical anastomosis in the contrast group as per the randomization. There were also more McKeown's oesophagectomies reformed. This caused an unequal distribution, which again could be a fallacy while interpreting the outcomes.

- There were no intra-thoracic anastomotic leaks in the study population. Hence, the importance of a routine upper GI contrast study in detecting such leaks could not be assessed.

9. CONCLUSIONS

- There was no increase in rate of morbidity or mortality in patients who did not routinely have a contrast swallow prior to initiation of feeds (Group B).
- Routine upper GI contrast studies after an oesophageal anastomosis did not offer any additional clinical benefit. In fact, two patients had aspiration of the contrast medium although there were no untoward consequences as a result of this.
- The use of an upper GI contrast study has a low sensitivity (13.60%) and hence it may not be of value as a screening test to detect a post-operative leak.
- The negative predictive value of this study is 45.70%. Hence, relying on this test to rule out a leak may give a false sense of security and may lead to missed leaks.
- Scheduling an upper GI contrast study on the 7^{th} post-operative day delayed the initiation of solid feeds by a day, adding to the length of hospital stay and therefore the cost incurred by the patient.
- In this study, the 2 patients with a neck anastomotic leak were not picked up by the contrast study. This therefore proves that a contrast study is not of much value in cervical oesophageal anastomosis.
- One patient had an abdominal anastomotic leak confirmed on contrast study. But this leak would have been clinically picked up even without a study. Therefore this underlines the fact that selective use of contrast study is more appropriate.
- Hence, the routine use of contrast study to rule out a post-operative oesophageal anastomotic leak can probably be abandoned. The need for an appropriate study can be made by the treating clinician, based on the level of clinical suspicion and the local expertise available.

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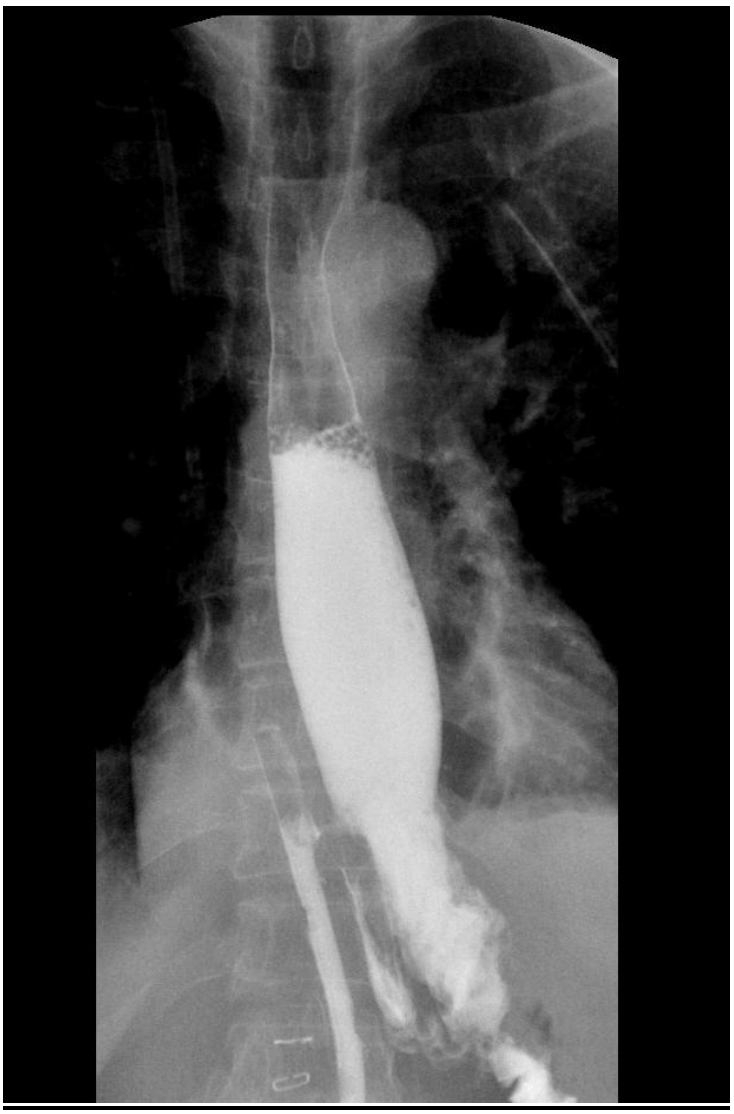
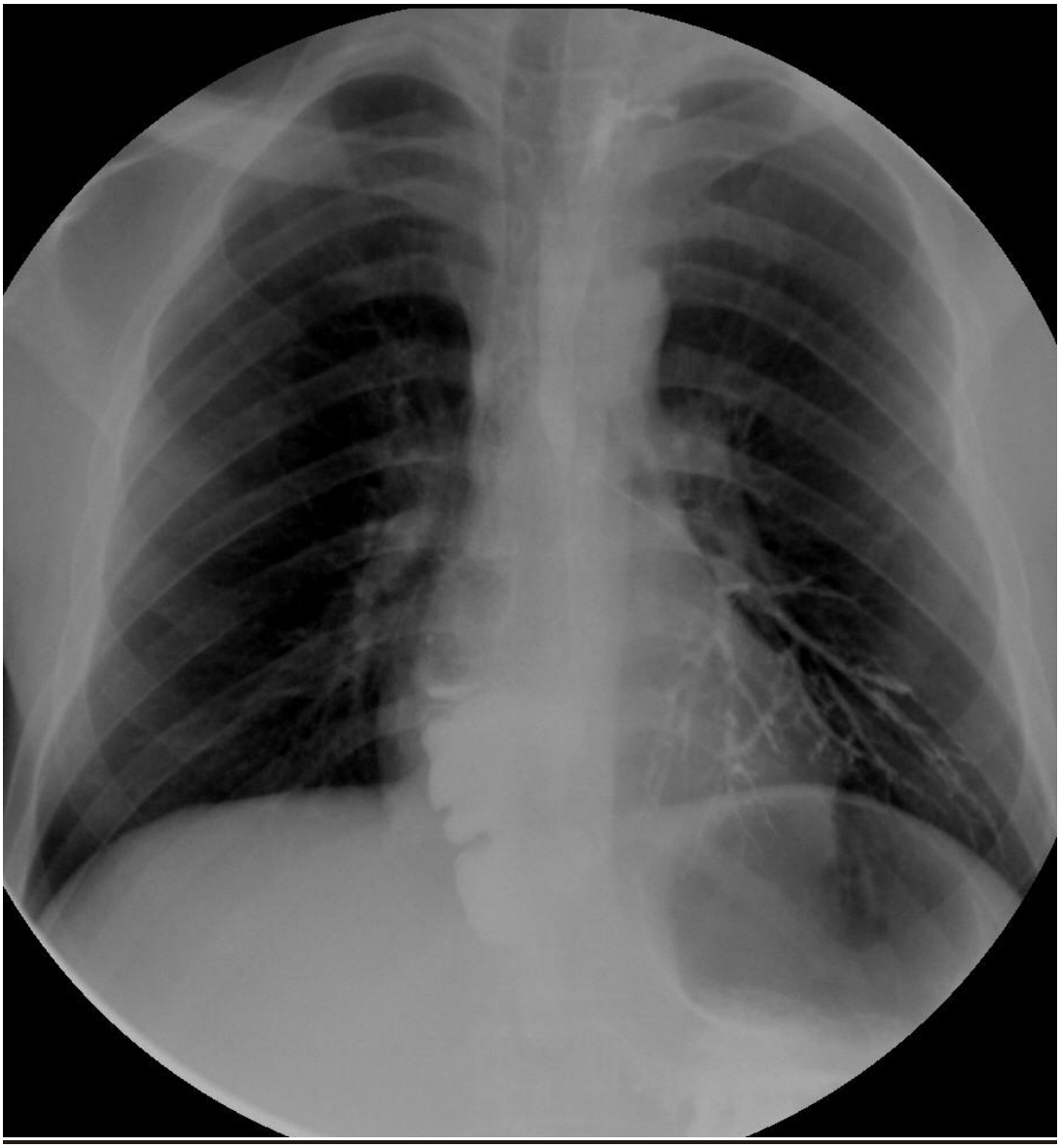
11. ANNEXURES

ANNEXURE 1



Oesophago-jejunal anastomotic leak with contrast extravasation and tracking into the intra-peritoneal drain.

ANNEXURE 2



Aspiration of contrast with opacification of the lower left tracheo-bronchial tree.

ANNEXURE 3 - INFORMED CONSENT SHEET

1. This study, in which you are being asked to participate, is being conducted to assess the need for a routine upper GI contrast study after an oesophageal anastomosis.

2. You will be randomly allocated into two groups under the study - group A and group B.
   If you come under group A you will be offered an upper GI contrast study which is an xray investigation, on the 7^{th} day after surgery and this is the existing practice. This x-ray test will be carried out free of cost if you wish to be part of the study.
   If you are allotted to group B you will not have a routine upper GI contrast study. Instead you will be monitored serially for clinical features of an anastomotic leak. On suspicion of a leak, your treating surgeon will do a CT scan or an upper GI contrast study to confirm this. The rest of the treatment will continue the same.

3. We do not anticipate any adverse effects in relation to not doing a routine contrast study. In the event of any unforeseen event happening, further treatment will be done without any additional cost for the patient.

4. As part of the study you will be monitored daily and your heart rate, blood pressure, temperature, respiratory rate, white cell counts etc. will be recorded.

5. The barium contrast study involves cost, manpower, irradiation hazard, allergic complications and a prolonged hospital stay. The main benefit from the study extends to the group of patients not undergoing the barium swallow thereby reducing their financial burden and probably cutting short their hospital stay. If it is proven that a routine upper GI contrast study is not required routinely after an esophageal anastomosis, this will be helpful to patients undergoing such operations in future.

6. The study details will be kept confidential in terms of personal information received from patients. Only the end results of the study will be published. The primary data collected will be kept in a database within General Surgery Unit 3, Christian Medical College, Vellore and will be accessible only to the doctors conducting the study.

7. Consenting to be part of the study is purely voluntary. You can withdraw from the study at any given point of time and no explanation needs to be offered regarding the same. The further course of treatment will follow the standard protocol and in no way will you be penalised for it.

8. You are eligible for the standard care offered to all patients in CMC, Vellore. None of the study patients will be deprived of the available therapies.

9. Any new information regarding the findings, if significant, will be notified to you.

10. The upper GI contrast study involves x-ray exposure to the foetus in case of pregnancy. Known pregnant ladies will not be involved in the study.

11. In the event of any further queries about the study, risks and benefits at any point of the study, you can contact Dr. Niveditha Shama at 0416 – 2282079.

Format of informed consent form for Subjects

Informed Consent form to participate in a research study

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name of the Witness: _____

ANNEXURE 4-INVESTIGATORS PROFORMA

STUDY TO ASSESS OUTCOME AFTER ESOPHAGEAL ANASTOMOSIS IN PATIENTS UNDERGOING BARIUM SWALLOW STUDY VERSUS PATIENTS NOT UNDERGOING THE BARIUM SWALLOW STUDY.

PATIENT'S NAME: AGE: SEX:

HOSPITAL NUMBER: D.O.B:

ADDRESS:

TELEPHONE: EMAIL ID:

DATE OF ADMISSION:

WEIGHT IN KG:

HEIGHT IN CM:

BMI:

DIAGNOSIS:

DATE OF DIAGNOSIS:

INITIAL INVESTIGATION LEADING TO DIAGNOSIS AND DATE:

1. ENDOSCOPY :
2. BARIUM SWALLOW/MEAL :
3. OTHERS: (PLEASE STATE) :

COMORBIDITIES:

1. DIABETES MELLITUS: Y/N
2. HYPERTENSION: Y/N
3. CARDIAC DISEASE: Y/N
4. RESPIRATORY DISEASE: Y/N
5. RENAL DISEASES: Y/N
6. OBESITY: Y/N
7. OTHERS:

SMOKER: Y/N DURATION:

ALCOHOLIC: Y/N DURATION:

PRE-TREATMENT STAGING IF MALIGNANT DISEASE:

TUMOR- T0, Tis, T1, T2, T3, T4

NODES- NO NODES / LOCOREGIONAL/DISTANT

METASTASIS – M0, M1

CHEMO/RADIOTHERAPY:

1. NEOADJUVANT CHEMO OR RADIOTHERAPY (PRE-OP)
2. ADJUVANT CHEMO OR RADIOTHERAPY (POST-OP)
3. DEFINITIVE CHEMO OR RADIOTHERAPY (WITHOUT OPERATION BUT FOR ATTEMPTED CURE)
4. PALLIATIVE CHEMO OR RADIOTHERAPY (WITHOUT OPERATION NOT FOR ATTEMPTED CURE)

RADIOTHERAPY:

DATE OF COMMENCEMENT: DATE OF COMPLETION:

WEEKS:

_____Gy _____FRACTIONS

RADIOTHERAPY FIELDS: Neck/ Thorax/ Abdomen / If elsewhere please specify:

DOSE: Low Dose / High Dose

COMPLICATIONS:

CHEMOTHERAPY:

DATE OF COMMENCEMENT: DATE OF COMPLETION:

AGENTS USED: 5FU / CISPLATIN/ CARBOPLATIN/ OTHERS

CYCLES:

DOSE: LOW DOSE/HIGH DOSE

COMPLICATIONS:

SURGICAL WORK-UP

ASA STATUS: 1/2/3/4/5

ANAESTHESIA

DOUBLE LUMEN TUBE: Y/N

THORACIC EPIDURAL: Y/N

ANALGESIA: PCA/EPIDURAL PERIOP/POSTOP/BOTH

EXTUBATED / INTUBATED AT THE END OF THE SURGERY:

ANY OTHER PROBLEMS (PLEASE SPECIFY):

ANAESTHETIC EVENTS: (OLA = ONE LUNG ANAESTHESIA)

PRE OLA:

HYPOXIA

HYPOTENSION

ARRHYTHMIA

ON OLA:

HYPOXIA

HYPOTENSION

ARRHYTHMIA

OLA POSSIBLE: Y/N; IF NO PLEASE SPECIFY WHY

DETAILS ABOUT SURGERY:

DATE OF RANDOMISATION:

PATIENT RANDOMISED TO GROUP A OR GROUP B:

**GROUP A: WILL UNDERGO THIN BARIUM SWALLOW/ GASTROGRAFFIN SWALLOW ON POST OPERATIVE DAY 7.

**GROUP B: WILL NOT UNDERGO THIN BARIUM SWALLOW/ GASTROGRAFFIN SWALLOW ON POST OPERATIVE DAY 7.

DATE OF SURGERY:

SURGERY PERFORMED WITH SITE OF ANASTOMOSIS DONE:

1. THORACO-ABDOMINAL
2. CERVICO ABDOMINAL
3. CERVICO THORACO ABDOMINAL
   TYPE OF ANASTOMOSIS:

1. HAND SEWN CONTINUOUS
2. HAND SEWN INTERRUPTED
3. STAPLED
   – STAPLER SIZE___

   CHEST: OPEN / LAPAROSCOPIC/ CONVERTED

   ABDOMEN: OPEN/LAPAROSCOPIC/CONVERTED

   ANTI-REFLUX PROCEDURE:

- NONE
- PARTIAL
- TOTAL
  FEEDING JEJUNOSTOMY: Y/N

   DRAINS: -CHEST: Y/N

   - ABDOMINAL: Y/N

   DRAINAGE PROCEDURE: NONE / PYLOROPLASTY/ PYLOROMYOTOMY/

   PYLOROMYOMECTOMY

   COMPLICATIONS/COMMENTS:

   DURATION OF SURGERY:

   ESTIMATED BLOOD LOSS IN ML:

   INTRA OP TRANSFUSION: Y/N IF YES NUMBER OF UNITS:

   POST OPERATIVE TRANSFUSION: Y/N IF YES NUMBER OF UNITS:

   POST OPERATIVE PERIOD:

   DURATION OF HOSPITAL STAY: POD___

   DURATION OF ICU STAY: POD___

   DURATION OF HDU STAY: POD___

   VENTILATED: Y/N IF YES, NUMBER OF DAYS:

   INOTROPES: Y/N IF YES, NUMBER OF DAYS:

   RE ADMISSION TO ICU/HDU: Y/N IF YES, PLEASE SPECIFY REASON:

RE INTUBATED: Y/N

ICU/HDU RE ADMISSION DETAILS:

RE OPERATION REQUIRED: Y/N.

DETAILS OF REOPERATION:

SERIAL MONITORING OF CLINICAL PARAMETERS:

	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7	POD 8	POD 9	POD 10
HR										
TEMP										
RR										
PERIT. RXN										
TC										
WOUN. INF										

HR-------HEART RATE

TEMP---TEMPERATURE

RR-------RESPIRATORY RATE

PERIT. RXN--- CLINICAL FEATURES SUGGESTIVE OF PERITONITIS LIKE ABDOMINAL TENDERNESS/GUARDING/ RIGIDITY.

TC--- TOTAL WBC COUNT

WOUND INF--- ANY ERYTHEMA/DISCHARGE/ POSITIVE CULTURES FROM WOUND ESPECIALLY IN NECK ANASTOMOSIS.

<u>FEATURES SUGGESTIVE OF ANASTOMOTIC LEAK (ANY 2):</u>

- tachycardia (heart rate > 100 beats per minute),
- fever (body temperature > 38°C),
- tachypnea (high respiratory rate), with greater than 20 breaths per minute
- local or generalized peritoneal reaction during physical examination

- leukocytosis (> 12 × 103/ml)
- Wound infection in case of neck anastomosis.

** KINDLY INFORM TREATING TEAM IN CASE ANY OF THE ABOVE FEATURES ARE SEEN.

*** IF ANY OF THE ABOVE DEVELOP THE PATIENT CAN UNDERGO ANY RADIOLOGICAL IMAGING TECHNIQUE AS DECIDED BY THE TREATING TEAM.

POST OPERATIVE DAY 7:

DATE:

UPPER GI CONTRAST STUDY: Y/N

IF YES, REPORT:

ANY OTHER RADIOLOGICAL INVESTIGATION CARRIED OUT:

DATE:

REASON:

REPORT:

DAY OF STARTING ORAL LIQUIDS: POD___

DATE OF STARTING SEMI SOLID DIET ORALLY: POD___

DATE OF DISCHARGE:

DAY OF DEATH:

DURATION OF HOSPITAL STAY:

IF MALIGNANT DISEASE:

HISTOPATHOLOGY REPORT:

TUMOR SITE: PROXIMAL THIRD / MIDDLE THIRD / DISTAL THIRD / CARDIA / GASTROESOPHAGEAL JUNCTION

TUMOR TYPE: SQUAMOUS CELL CARCINOMA / ADENOCARCINOMA / MIXED / OTHER

BARRETS': PRESENT / ABSENT

NODE HARVEST NUMBER:

PROXMIAL MARGINS: INVOLVED / FREE OF TUMOR, ____MM

DISTAL MARGINS: INVOLVED / FREE OF TUMOR, ____MM

TUMOR DIFFERENTIATION: WELL DIFFERNTIATED / MODERATELY DIFFERNTIATED/

MODERATE TO POORLY DIFFERNTIATED / POORLY DIFFERNTIATED

BASED ON HISTOLOGY AND SURGICAL FINDINGS:

- PROBABLE CURATIVE RESECTION
- POSSIBLE CURATIVE RESECTION
- PALLIATIVE RESECTION

POST OPERATIVE TNM STAGING:

TUMOR- T0, Tis, T1, T2, T3, T4

NODES- NO NODES / LOCOREGIONAL/DISTANT

METASTASIS – M0, M1

CLAVIEN-DINDO CLASSIFICATION OF COMPLICATIONS

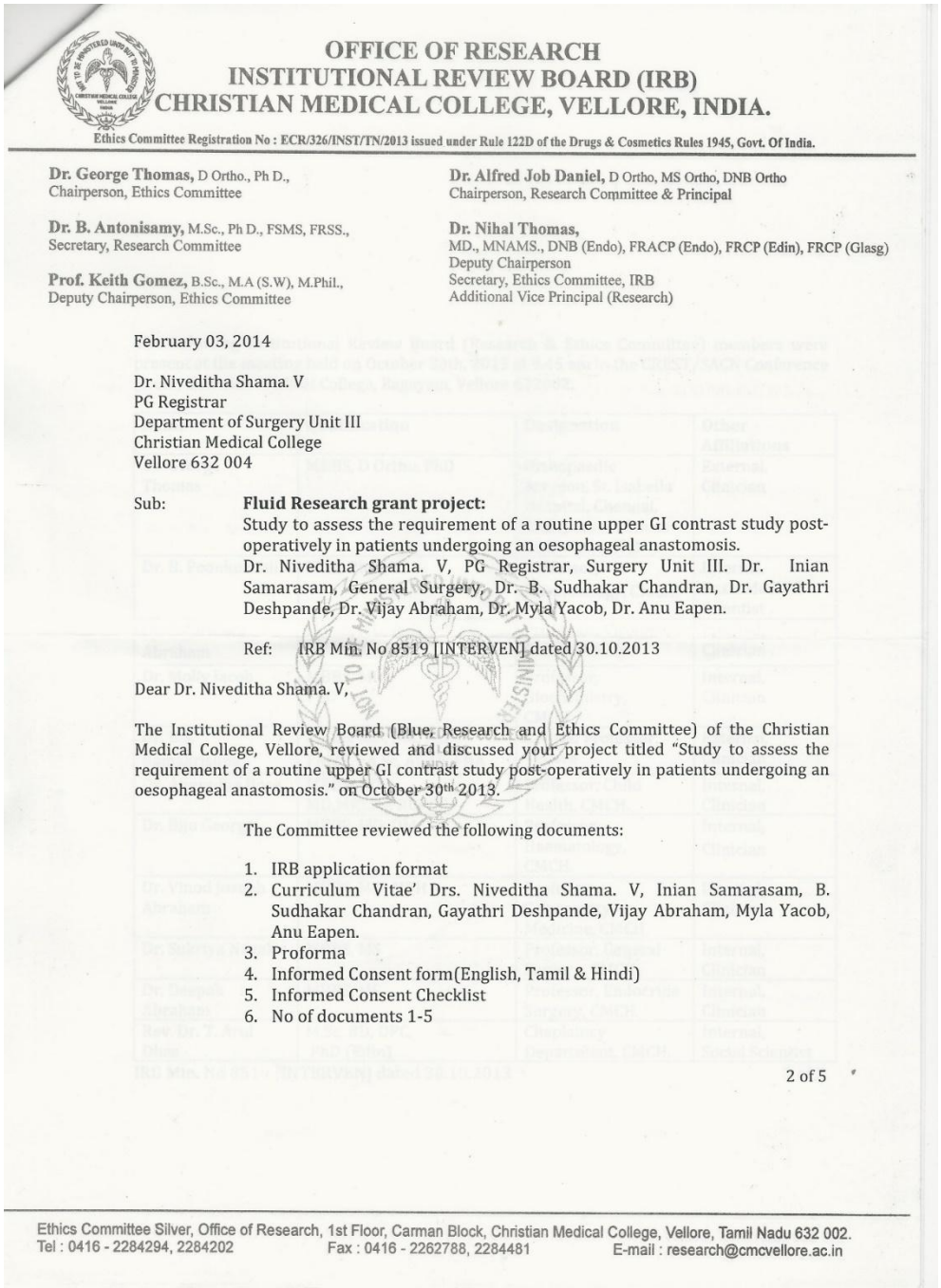
COMPLICATIONS:

GRADE I:	FEVER CONTROLLED WITH ANTIPYRETICS ONLY: Y/N
	SEVERE PAIN CONTROLLED WITH ANALGESICS: Y/N
	WOUND INFECTION/DISCHARGE OPENED AT BEDSIDE: Y/N
	PARALYTIC ILEUS: Y/N
GRADE II:	WOUND INFECTION/SEPSIS REQUIRING ANTIBIOTIC THERAPY: Y/N
	CHEST INFECTION MANAGED WITH ANTIBIOTIC THERAPY: Y/N
	ABDOMINAL INFECTION MANAGED WITH ANTIBIOTIC THERAPY: Y/N
	POST OPERATIVE BLOOD TRANSFUSIONS: Y/N
	TOTAL PARENTERAL NUTRITION: Y/N
	ANASTOMOTIC LEAK MANAGED WITH ANTIBIOTICS ONLY: Y/N
GRADE III:	ANASTOMOTIC LEAK WITH ENDOSCOPIC INTERVENTION NEEDED: Y/N.
	ANASTOMOTIC LEAK WITH RADIOLOGICAL INTERVENTION NEEDED: Y/N.
	ANASTOMOTIC LEAK WITH SURGICAL INTERVENTION NEEDED: Y/N.
	OTHER COMPLICATIONS REQUIRING ENDOSCOPIC INTERVENTION / RADIOLOGICAL INTERVENTION / SURGICAL INTERVENTION ; Y/N: PLEASE SPECIFY
GRADE IIIA	IF NOT REQUIRING GENERAL ANAESTHESIA
GRADE IIIB	IF REQUIRING GENERAL ANAESTHESIA
GRADE IV A	RESPIRATORY FAILURE ONLY: Y/N OR RENAL FAILURE ONLY: Y/N

GRADE IV B	RESPIRATORY FAILURE: Y/N
	RENAL FAILURE: Y/N
	SEPTIC SHOCK: Y/N
	MULTI ORGAN DYSFUNCTION: Y/N
GRADE V:	DEATH OF THE PATIENT

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are as follows: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

ANNEXURE 5- APPROVAL FROM INSTITUTIONAL REVIEW BOARD



OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No : ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

Dr. George Thomas, D Ortho., Ph D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

February 03, 2014

Dr. Niveditha Shama. V
PG Registrar
Department of Surgery Unit III
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project:**
Study to assess the requirement of a routine upper GI contrast study post-operatively in patients undergoing an oesophageal anastomosis.
Dr. Niveditha Shama. V, PG Registrar, Surgery Unit III. Dr. Inian Samarasam, General Surgery, Dr. B. Sudhakar Chandran, Dr. Gayathri Deshpande, Dr. Vijay Abraham, Dr. Myla Yacob, Dr. Anu Eapen.

Ref: IRB Min. No 8519 [INTERVEN] dated 30.10.2013

Dear Dr. Niveditha Shama. V,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Study to assess the requirement of a routine upper GI contrast study post-operatively in patients undergoing an oesophageal anastomosis." on October 30th 2013.

The Committee reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Drs. Niveditha Shama. V, Inian Samarasam, B. Sudhakar Chandran, Gayathri Deshpande, Vijay Abraham, Myla Yacob, Anu Eapen.
3. Proforma
4. Informed Consent form(English, Tamil & Hindi)
5. Informed Consent Checklist
6. No of documents 1-5

2 of 5

Ethics Committee Silver, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. George Thomas, D Ortho., Ph D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Secretary IRB (EC)& Dy. Chairperson (IRB), Prof. of Endocrinology & Addl. Vice Principal(Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

The study will need to be submitted to a three monthly data-safety monitoring board (DSMB) review with duly filled in form found in the link.
http://172.16.11.136/Research/IRB_Polices.html

Fluid Grant Allocation:

A sum of 80,000 INR (Rupees Eighty Thousand only) will be granted for 2 years.

Yours sincerely

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr. Inian Samarasam, General Surgery, CMC

IRB Min. No 8519 [INTERVEN] dated 30.10.2013 5 of 5

CHRISTIAN MEDICAL COLLEGE, VELLORE

AGREEMENT TO BE SIGNED BEFORE RELEASE OF ANY RESEARCH GRANT

*****

1. I understand that the research grant is sanctioned only for the specific project approved by the Institutional Review Board and should be used exclusively for this project

2. I note that the project will become operational with effect from the date on which the grant is received, and I agree to complete it within the stipulated time of 2 years.

3. I agree to submit promptly and regularly, the periodical (Half Yearly for One Year Project/Annually for Two years project) reports and the final report of the work done, in the approved format.

4. If I plan to leave the institution before the completion of the project. I will submit a complete and detailed report of the work done by me on the project till the date of relief and transfer the project, either to the Guide or to the Co-Investigator for completion and submission of the Final Report.

5. I agree that any publication arising out of this project will carry an acknowledgement of the financial support of the Christian Medical College Fluid Research Fund

Fluid Grant Allocation:

A sum of 80,000/- INR (Rupees Eighty Thousand only) will be granted for 2 years.

V. Niveditha Shama

PRINCIPAL

Dr. Niveditha Shama. V
Department of Surgery Unit III

Dr. Inian Samarasam
Department of Surgery

Project Title: Study to assess the requirement of a routine upper GI contrast study post-operatively in patients undergoing an oesophageal anastomosis.

Ref: IRB Min. No 8519 [INTERVEN] dated 30.10.2013

ANNEXURE 6 – DATA SHEETS

id	name	h	age	sex	ht	wt	bmi	smok	alco	diag	site	tnm	ptnm	nac	nar	dol	dos	sih	asa
1	JAYANANI	774031F	49	0	170	50	17.3	TRUE	TRUE	1	2	T3 N1 MO	YP T2 N0 M	TRUE	TRUE	8	10	10	2
2	SACHIN KI	788203f	23	0	160	15	19.5	FALSE	FALSE	3	3	99	99	FALSE	FALSE	6	9	11	1
3	GURUSELV	864215F	53	1	156	58	23.8	FALSE	FALSE	1	6	T4a N3a M	P T4a N3a	FALSE	FALSE	8	9	15	1
4	RAMANI K	869904f	65	0	157	54	21.9	FALSE	FALSE	1	4	T3 N2 M0	P T3 N2 M	FALSE	FALSE	6	9	15	1
5	GIRISH	803575F	41	0	164	57	21.2	FALSE	FALSE	1	4		YP T2 N0 M	TRUE	FALSE	6	9	12	1
6	MAHENDF	833944F	52	0	175	50	16.3	TRUE	FALSE	2	3	T3 N0 M0	99	TRUE	FALSE	5	8	20	2
7	PAPIYA HA	839346F	31	1	148	38	17.3	FALSE	FALSE	3	1	99	99	FALSE	FALSE	99	99	17	1
8	MURALI	523209C	44	0	172	62	21	TRUE	TRUE	2	2	99	YP T3 N1 M	TRUE	TRUE	9	11	12	1
9	RABINDRA	826751F	40	0	165	67	24.6	FALSE	FALSE	1	4	T3 N0 M0	PT3 NO M	TRUE	FALSE	8	9	13	1
10	SANI MAY	002488G	48	1	153	47	20.1	FALSE	FALSE	1	6	99	YP T4A N3	TRUE	FALSE	5	7	11	1
11	RINA MUT	842477f	61	1	153	45	19.2	FALSE	FALSE	2	2	99	T0 NO MX	TRUE	TRUE	7	9	15	2
12	ATIAR SUT	839641F	49	0	999.99	56	99.99	FALSE	FALSE	2	2	99	YP T0 N0 M	TRUE	TRUE	4	6	13	2
13	SETTU	018874G	64	0	169	45	15.8	TRUE	TRUE	1	6	99	P T3 N3A M	FALSE	FALSE	6	8	12	1
14	SUBASH C	872793F	63	0	150	53	23.6	TRUE	FALSE	2	3	99	99	TRUE	TRUE	7	9	12	2
15	MD. IBRAI	885128F	48	0	162	51	19.4	FALSE	FALSE	2	2	99	yp T1A N0	TRUE	TRUE	7	12	15	1
16	SRINIVAS/	878852F	50	0	165	61	22.4	FALSE	FALSE	2	2	99	YP T0 NO I	TRUE	TRUE	7	0	12	1
17	THANGAV	229956B	56	0	165	89	32.7	FALSE	TRUE	1	3	99	YP T2 NO I	TRUE	FALSE	5	7	10	2
18	PARTHASA	910072F	42	0	162	41	15.6	TRUE	TRUE	3	2	99	99	FALSE	FALSE	11	13	15	2
19	ANNAMM	050731G	66	1	153	61	26.1	FALSE	FALSE	2	2	T3 NO MO	YP T1A N1	TRUE	TRUE	6	8	12	2
20	PHILIP K.M	057521G	65	0	152	55	23.8	FALSE	FALSE	1	4	99	YP T3 N1 M	TRUE	FALSE	6	9	17	2
21	DWIJAPAL	352393F	70	0	170	61	21.1	FALSE	FALSE	5	6	99	99	TRUE	FALSE	5	7	10	2
22	MISBA FA	796628F	19	1	160	40	15.6	FALSE	FALSE	3	1	99	99	FALSE	FALSE	10	12	14	1
23	NITISH KA	907438F	38	0	158	48	19.2	FALSE	FALSE	3	2	99	99	FALSE	FALSE	18	20	18	2
24	PRIOTOSH	066811G	28	0	161	44	17	FALSE	FALSE	1	4	99	YP T2 NO I	TRUE	FALSE	5	8	16	1
25	KISHORE T	033270G	49	0	166	58	21	TRUE	FALSE	2	2	99	YP T2 N0 M	FALSE	TRUE	5	7	12	1
26	SANKAR D	835437F	34	0	165	51	18.7	TRUE	FALSE	3	2	99	99	FALSE	FALSE	6	8	10	1
27	MAMTAZ I	098385G	45	1	148	56	25.6	FALSE	FALSE	1	6	T4A N2 M(	YP T4A N2	TRUE	FALSE	6	8	14	2
28	MD. RAHM	055399G	51	0	169	61	21.4	TRUE	TRUE	2	2	99	YP T0 N0 M	TRUE	TRUE	4	5	9	2
29	ABU KALA	085961G	35	0	170	65	22.5	FALSE	FALSE	1	5	99	YP T4A N2	TRUE	TRUE	6	8	9	2
30	DEVARAJ/	063702G	64	0	167	59	21.2	FALSE	FALSE	1	4	T4 N2 M0	pT3 N1 MX	TRUE	FALSE	7	9	13	1
31	ARDHEND	090632G	74	0	162	57	21.7	TRUE	FALSE	2	2	99	YP T3 N0 M	TRUE	TRUE	6	0	13	2
32	SANAT SIN	154789G	55	0	164	50	18.6	FALSE	FALSE	1	5	99	YP T4A N2	FALSE	FALSE	5	7	8	1
33	SHEMLAD	930564F	43	0	160	51	19.9	TRUE	FALSE	2	3	99	YP T3 NO I	TRUE	TRUE	6	8	12	1
34	DOLLY KH	938289F	60	1	152	45	19.5	TRUE	FALSE	1	6	T1 NO MO	YP T3 NO I	FALSE	FALSE	6	9	12	2
35	PYNAPALA	103787G	43	0	156	49	20.1	TRUE	TRUE	2	2	99	yp T2 N0 M	TRUE	TRUE	9	12	16	1
36	THAMIYA	249632F	56	1	162	52	20.1	FALSE	FALSE	2	3	99	yp T2 N0 M	TRUE	FALSE	10	12	25	2
37	MD SOLAI	176102G	25	0	158	55	22	FALSE	FALSE	4	2	99	99	FALSE	FALSE	6	8	11	1
38	NAKSHATI	185825G	60	0	158	55	21	TRUE	FALSE	5	5	99	p T4 N0 M	FALSE	FALSE	5	8	9	1
39	BHOLA SA	120287G	58	0	165	55	20.2	FALSE	FALSE	1	4	99	yp T3 N3 M	TRUE	FALSE	6	8	8	1
40	SHASHIKA	929757F	50	1	149	34	15.3	FALSE	FALSE	2	4	99	yp T3 N1 M	TRUE	FALSE	15	17	23	2

surg	group	ugic	spod	result	soa	toa	fj	cd	ad	dur	icu	vent	readm	reint	reop	temper	hr	wi	rr
MCKEOWI	B	FALSE		FALSE	1	1	TRUE	TRUE	FALSE	5	2	0	FALSE	FALSE	FALSE	101.2 F ON	100 BPM C	FALSE	28 ON POI
GASTRIC F	A	FALSE		FALSE	1	3	TRUE	TRUE	FALSE	6	1	0	FALSE	FALSE	FALSE	AFEBRILE	NORMAL	FALSE	NORMAL
TOTAL GA	B	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	3.45	0	0	FALSE	FALSE	FALSE	100.2 F ON	100 BPM C	FALSE	NORMAL
TOTAL GA	A	TRUE	7	FALSE	3	3	TRUE	FALSE	TRUE	6	0	0	FALSE	FALSE	FALSE	99.8 F ON	NORMAL	TRUE	NORMAL
IVOR LEW	A	TRUE	8	FALSE	2	3	TRUE	TRUE	TRUE	4	3	0	FALSE	FALSE	FALSE	101 F ON I	94 BPM OI	FALSE	NORMAL
MCKEOWI	A	TRUE	8	FALSE	1	3	TRUE	TRUE	TRUE	99.99	2	1	FALSE	TRUE	FALSE	NORMAL	130 ON PO	FALSE	40 ON POI
COLON PL	B	FALSE		FALSE	1	3	TRUE	FALSE	TRUE	99.99	1	1	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	3	TRUE	TRUE	TRUE	4.45	2	1	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
IVOR LEW	A	TRUE	8	FALSE	2	3	TRUE	TRUE	TRUE	5		0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	B	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	4.3	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	A	TRUE	6	FALSE	1	3	TRUE	TRUE	FALSE	99.99	2	0	FALSE	FALSE	FALSE	NO FEVER	NORMAL	FALSE	24
MCKEOWI	B	FALSE		FALSE	1	1	FALSE	TRUE	TRUE	99	0	0	FALSE	FALSE	FALSE	101 F ON I	100	FALSE	NORMAL
TOTAL GA	A	TRUE	8	FALSE	3	3	TRUE	FALSE	TRUE	4	0	0	FALSE	FALSE	FALSE	100 AND 1	100 AND 9	FALSE	24
MCKEOWI	A	FALSE		FALSE	1	3	TRUE	TRUE	FALSE	4.45	2	0	FALSE	FALSE	FALSE	99 F ON P(	80 ON POI	FALSE	NORMAL
MCKEOWI	A	TRUE	7	FALSE	1	3	TRUE	TRUE	FALSE	99	3	1	FALSE	FALSE	FALSE	NORMAL	NORMAL	TRUE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	3	TRUE	TRUE	TRUE	4.4	0	0	FALSE	FALSE	FALSE	100 ON PO	90 ON POI	TRUE	NORMAL
IVOR LEW	B	FALSE		FALSE	2	3	TRUE	TRUE	TRUE	99.99	2	1	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
IVOR LEW	A	TRUE	9	FALSE	2	3	TRUE	TRUE	FALSE	5			FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	3	TRUE	TRUE	TRUE	5.45	5	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL

IVOR LEW	A	TRUE	9	FALSE	2	3	TRUE	TRUE	TRUE	4.45	3	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	A	TRUE	7	FALSE	3	3	FALSE	FALSE	TRUE	99	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
COLON PL	B	FALSE		FALSE	1	3	TRUE	FALSE	TRUE	99	3	0	FALSE	FALSE	FALSE	101.4 ON I	98 BPM	FALSE	30 ON POI
COLON PL	A	FALSE		FALSE	1	3	TRUE	FALSE	TRUE	99	2	0	FALSE	TRUE	TRUE	104.6 ON I	110 BPM C	FALSE	30 ON POI
IVOR LEW	A	TRUE	8	FALSE	2	3	TRUE	TRUE	TRUE	99.99	2	0	TRUE	FALSE	FALSE	NORMAL	100 ON PC	TRUE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	3	TRUE	TRUE	TRUE		6	1	FALSE	FALSE	FALSE	100 ON PC	84 ON POI	TRUE	NORMAL
COLON PL	A	TRUE	8	FALSE	1	3	TRUE	TRUE	TRUE	99.99	2	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	B	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	4	2	0	FALSE	FALSE	FALSE	101 F ON I	120 BPM C	FALSE	20 ON POI
MCKEOWI	A	TRUE	6	FALSE	1	3	TRUE	TRUE	TRUE	99.99	1	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	A	TRUE	8	FALSE	3	3	TRUE	FALSE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
IVOR LEW	A	TRUE	9	FALSE	2	3	TRUE	TRUE	TRUE	4.45	1	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	3	TRUE	TRUE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	100 ON PC	80 ON POI	TRUE	NORMAL
TOTAL GA	B	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	4	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	B	FALSE		FALSE	1	1, 3	TRUE	TRUE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	B	TRUE	8	FALSE	3	3	TRUE	FALSE	TRUE	4.3	2	0	TRUE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
MCKEOWI	A	FALSE		FALSE	1	3	TRUE	TRUE	FALSE	99.99	9	0	FALSE	FALSE	FALSE	NORMAL	120 BPM C	FALSE	30 ON POI
MCKEOWI	B	FALSE		FALSE	1	1, 2	TRUE	TRUE	FALSE	99.99	2	0	TRUE	FALSE	FALSE	100 ON PC	90 ON POI	FALSE	NORMAL
MCKEOWI	A	FALSE		FALSE	1	3	TRUE	TRUE	FALSE	99.99	3	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	B	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	A	FALSE		FALSE	3	3	TRUE	FALSE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	NORMAL	NORMAL	FALSE	NORMAL
TOTAL GA	A	TRUE	8	TRUE	3	2	TRUE	FALSE	TRUE	99.99	0	0	FALSE	FALSE	FALSE	100 ON PC	90 BPM OI	FALSE	NORMAL

peri	tc	otrad	indic	result1	compl	cdg	fhpe
FALSE	9100/CU.N	CHEST XR/	PERSISTEN	NORMAL	CHEST INF	2	2
FALSE	15100 /CU	NONE	NONE	NONE	NONE	0	3
FALSE	16980 /CU	CECT ABD	FEVER AN	NORMAL	URINARY	2	1
FALSE	12,300 / C	NONE	NONE	NONE	WOUND I	1	1
FALSE	14700 CU/	CHEST X-R	PNEUMON	NORMAL	PNEUMON	2	1
FALSE	3600 / CU.	CECT THO	HYPOTEN	NORMAL	RESPIRAT	4	99
FALSE	9100 / CU.	CHEST X-R	ASPIRATI	NORMAL	FAILURE C	F PROCED	FIBROSIS
FALSE	9100 / CU.	CHEST X-R	COUGH	NORMAL	NONE	0	2
FALSE		CHEST X-R	FOR ASSE	PROLONG	NIL	0	
FALSE	6600 /CU.I	NONE	NONE	NONE	NONE	0	1
FALSE	12,500 CEL	CHEST XR/	PNEUMON	PNEUMON	PNEUMON	2	99
FALSE	13700 / CL	CHEST X-R	FEVER	NORMAL	URINARY	2	99
FALSE	13,600 / C	CHEST X-R	COUGH W	PNEUMON	PNEUMON	2	1
FALSE	11,400 / C	CHEST XR/	COUGH AI	PNEUMON	PNEUMON	2	99
FALSE	17,000 / C	CHEST XR/	CHEST DR/	NORMAL	ANASTOM	1	2
FALSE	8970 / CU.	CHEST X-R	AFTER CHI	NORMAL	ANASTOM	1	99
FALSE	999999995	CHEST X-R	AFTER CHI	NORMAL	NONE	0	1
FALSE	11, 300 / C	CHEST XR/	AFTER CHI	NORMAL	NONE	0	3
FALSE	7100 / CU.	CHEST X-R	AFTER CHI	NORMAL	LEFT VOCA	1	2

FALSE	10,800 / C	CHEST X-R	AFTER CHI	NORMAL	PERSISTEN	1	1
FALSE	9999999	NONE	NONE	NONE	NONE	0	5
FALSE	5200/ CU.I	CHEST XR/	FEVER AN	PNEUMON	PNEUMON	1	FIBROSIS
TRUE	4100 / CU.	CECT ABD	FEVER AN	FREE FLUI	REEXPLOR	3	FIBROSIS
FALSE	11700 / CU	CHEST X R	AFTER CHI	NORMAL	WOUND D	1	1
FALSE	6400 / CU.	CHEST X-R	AFTER CHI	NORMAL	WOUND I	1	2
FALSE	9800/CU.N	CHEST XR/	AFTER CHI	NORMAL	ANASTOM	1	FIBROSIS
FALSE	21,200 / C	USG ABDC	ABDOMIN	ACUTE CH	ACUTE CH	2	1
FALSE	5600 /CU.I	CHEST X-R	AFTER CHI	NORMAL	NONE	0	NO TUMO
FALSE	19600 / CU	CHEST X-R	COUGH	NORMAL	NONE	0	1
FALSE	10,600 / C	CHEST X-R	AFTER CHI	NORMAL	NONE	0	ADENOCA
TRUE	6200 / CU.	CHEST X-R	AFTER CHI	NORMAL	OESOPHA	2	2
FALSE	99999	NONE	NONE	NONE	NONE	0	1
FALSE	8000 / CU.	CHEST XR/	AFTER CHI	NORMAL	NONE	0	2
FALSE	5500 / CU.	NONE	NONE	NONE	UTI, PARA	2	1
FALSE	6900 / CU.	CHEST XR/	PERSISTEN	PLEURAL E	PNEUMON	2	2
FALSE	12,500 / C	CECT ON F	PERSISTEN	MEDIASTI	MEDIASTI	3	2
FALSE	99999	CHEST X R	AFTER CHI	NORMAL	NONE	0	4
FALSE	99999	NONE	NONE	NONE	NONE	0	5
FALSE	99999	NONE	NONE	NONE	NONE	0	1
FALSE	5000 CELL	CHEST XR/	PLEURAL E	PLEURAL E	ANASTOM	2	2